Annotated Clinical Review of Biological License Application

Product:	Palivizumab (MEDI-493) (humanized monoclonal antibody to respiratory syncytial virus)
BLA number:	97-1359
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Today's date:	April 30, 1998 Dwaine Rieves 5-1-98
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1.0.0 INTRODUCTION:

This document is this medical officer's review of background information and data contained in the BLA application for MEDI-493. MEDI-493 is a monoclonal antibody proposed for use in the prophylaxis of severe respiratory syncytial virus (RSV) infections in infants and children.

1.1.0 Materials reviewed:

This review is a summary of information and data contained in the BLA submission, the background Investigational New Drug Applications (IND numbers [redacted], pertinent clinical and scientific publications, IND applications for similar products [redacted] nd minutes from the 1993 and 1995 meetings of the Blood Products Advisory Committee (BPAC). The BPAC discussions of 1993 and 1995 concerned a polyclonal gammaglobulin product (RespiGam™) which is currently marketed by MedImmune, Inc. for prophylaxis of RSV infections.

[redacted] s an IND containing protocols which study the use of MEDI-493 in prophylaxis. IND numbe [redacted] oncerns the use of MEDI-493 in the treatment of RSV infections.

1.2.0 Indication:

The sponsor proposes the following as the indication:

"Palivizumab is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV). Palivizumab has been demonstrated to be safe and effective in reducing the incidence and days of RSV hospitalization and the severity of RSV illness in infants and children with a history of premature birth (≤ 35 weeks gestation) with or without bronchopulmonary dysplasia (BPD) ."

Comment: The above indication is similar to the current indication for RespiGam™ (the sponsor's licensed polyclonal gamma globulin product). "RespiGam™ is indicated for the prevention of serious lower respiratory tract infection caused by RSV in children under 24 months of age with bronchopulmonary dysplasia (BPD) or a history of premature birth (≤ 35 weeks gestation). RespiGam™ has been demonstrated to be safe and effective in reducing the incidence and duration of RSV hospitalization and the severity of RSV illness in these high risk infants."

The main difference is that the sponsor deletes the description of the target patient population in the introductory sentence-- "infants and children under 24 months of age with BPD or a history of premature birth (≤ 35 weeks gestation)." Actually this is also a generalization of the clinical trial data since the pertinent studies for RespiGam™ studied children with BPD ≤ 24 months of age and those with a history of prematurity who were ≤ six months of age at the time of enrollment. Nevertheless, the sponsor's first sentence of the indication should be modified to include the target patient population defined by safety and efficacy studies (CFR 201.57 (c) (3) (1)).

1.3.0 Clinical background:

RSV, an enveloped RNA virus of the paramyxovirus family, is a common human respiratory pathogen and is the major cause of respiratory tract illness in children.[1] RSV infection is generally acquired via particle inoculation of the nasal or lachrymal mucosa from large droplets (fomites or contact with contaminated secretions) . Most RSV infections manifest as respiratory tract disease. Asymptomatic infection is uncommon. Severe RSV disease usually manifests as bronchiolitis or pneumonia and is primarily a

[1]Walsh, E, McConnochie, K, Long, C, Hall, C. Severity of respiratory syncytial virus infection is related to virus strain. J Infect Dis. 1997;175:814-20.

disease of infants and immunosuppressed individuals.[2] Infants at greatest risk for RSV include those with a history of prematurity, immunodeficiency, congenital heart disease or chronic lung disease. It is estimated that 50-70% of all infants experience RSV infection in the first year of life and almost all are infected by two years of age. RSV causes more than 90,000 hospitalizations and 4,500 deaths in the United States annually.[3] It is estimated that several hundred thousand infants in the United States are at risk for severe RSV infection, although severe respiratory disease will develop in less than one percent of these infants.[4]

1.3.1 RSV Biology:

RSV belongs to the genus *pneumonvirus* of the Paramyxoviridae family. The virus is an enveloped, single negative-stranded RNA virus of medium size (120-300 nm). The RSV genome encodes for 10 quintessential viral proteins. Two of these proteins, the F (fusion) and G (attachment) proteins, are surface glycoproteins and are important in infecting cells. The G protein appears to function in mediating cellular attachment and extensive strain variations in its amino acid sequence have been described. The F protein is believed to function in syncytial formation and its amino acid sequence is highly conserved across viral strains. Monoclonal antibodies have identified two main RSV strains, A and B. The major antigenic differences between these two strains have been related to G protein differences. There is approximately 92% amino acid homology of the F protein between the A and B strains. Multiple substrains of RSV have also been identified. A strain infections have generally been associated with more severe respiratory disease than B strain infections.

Adult volunteer studies have shown that experimental infection occurs after an average incubation of five days (range two to eight days). The virus infects cells of the respiratory mucosa and spreads by fusion of infected cells. Virus is shed for six to eight days following infection. Airway epithelial infection results in inflammation and airway narrowing. This pathogenesis usually results in bronchiolitis and pneumonia in infants and bronchitis and upper respiratory infection in older humans. For unclear reasons, RSV infection may occur in the presence of maternally acquired RSV antibodies, although anecdotal evidence suggests the infections are less severe. In general, the level of serum antibody has not been shown to be clearly predictive of the risk of infection, severity of illness or recovery in either adults or children. However, adults experimentally challenged with RSV have shown infection rates which correlated with the serum antibody level. Additionally, breast feeding of infants has been correlated with less severe RSV infections.

Primary infection with RSV is not protective against subsequent infections. The immunologic response to RSV is an area of intense investigation, especially since early studies showed adverse experiences following RSV vaccination. Concern that an antibody response to RSV may be harmful developed following the experience with a formalin inactivated RSV vaccine in the early 1960's. This vaccine was immunogenic but failed to protect against RSV infection. Indeed, the immunized subjects experienced more severe RSV infections. Subsequent studies of the immunized patients showed that the antibody response to the F protein was lower in the immunized patients than the control patients and the antibodies were nonneutralizing. This finding has been attributed to an alteration of the RSV epitopes by formalin resulting in the generation of nonprotective antibodies.

The clinical manifestations of RSV infection vary by age. Infection in young children may manifest as lower

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[2]The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics 1997;99:93-99.

[3]Hall, C. Respiratory syncytial virus. What we know now. Contemp Pediatr. November 1993:2-11.

[4]Committee on Infectious Diseases, Committee on Fetus and Newborn. Respiratory syncytial virus immune globulin intravenous: indications for use. Pediatrics 1997;4:645-650.

respiratory tract diseases, such as pneumonia, bronchiolitis, tracheobronchitis or upper respiratory tract disease and otitis media. Infants usually manifest pneumonia or bronchiolitis in response to RSV infection. Two to four days after exposure to RSV, bronchiolitis and pneumonia develops in infants and manifests as fever (38° to 40° C) and cough. Tachypnea and labored respirations follow and hypoxemia is common among those infants requiring hospitalization. In most infants the duration of the illness is seven to 21 days and hospitalization, if required, averages four to seven days. Infants under the age of six months are at highest risk for pneumonia and bronchiolitis. Treatment for RSV bronchiolitis and pneumonia includes general respiratory care procedures as well the use of ribavirin in patients at high risk for severe RSV infection or those severely ill. Ribavirin is a nucleoside analogue that is delivered by aerosol administration.

Comment: Ribavirin was approved by the FDA in 1986 for aerosol treatment of serious RSV infections in hospitalized children. The drug is delivered as an aerosol over a prolonged period of time. The aerosol is administered for 12 to 20 hours per day usually for 3 to 5 days. Because of the logistical considerations in dosing and cost the American Academy of Pediatrics initially recommended only selective use of ribavirin--for patients at high risk for complications (including those with BPD, cystic fibrosis and immunodeficiency; those with hypoxemia; those requiring mechanical ventilation). The Academy also recommended that pregnant women be prohibited from caring for infants receiving ribavirin (because of potential terratogenicity).[5] After subsequent studies showed very questionable efficacy of ribavirin, the Academy revised its recommendations to state that ribavirin is to be "considered " for use in patients at high risk for complications (rather than explicitly recommending its use, as the 1993 statement declared).[6] For these reasons the use of ribavirin is regarded as a therapeutic option that requires a considerable degree of clinical judgement and is not uniformly utilized in infants hospitalized with RSV.

Infections in older children and adults usually manifest with cough and coryza. Fever and conjunctivitis are also commonly found. RSV tends to cause more severe and prolonged illness in adults than other common viral respiratory pathogens such as rhinovirus. RSV is commonly spread within a family and is highly contagious. The virus may survive in bodily secretions and nosocomial outbreaks among health care workers has been reported.

Comment: Infants hospitalized with RSV are generally cared for with the use of respiratory precautions but the use of gowns and gloves for routine nursing care appears to be inconsistent among hospitals.[7]

1.3.2 RSV Immunoprophylaxis:

Studies in cotton rats showing prevention of RSV infection by immunoprophylaxis prompted the sponsor to develop RSV IVIG (RespiGam™). RespiGam™ is a product prepared from hyperimmune human serum and was licensed in January, 1996.

There were primarily two phase 3 studies utilized to support RespiGam™ licensure. The first of these was

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[5]Committee on Infectious Diseases. Use of Ribavirin in the treatment of respiratory syncytial virus infection. Pediatrics 1993; 92: 501-503.

[6]Committee on Infectious Diseases. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. Pediatrics. 1996. 97:137-140.

[7] Langley, et.al. Nosocomial respiratory syncytial virus infection in Canadian pediatric hospitals: a pediatric investigators collaborative network on infections in Canada study. Pediatrics. 1997; 100:943-946.

the PREVENT study and is described below.[8]

Comment: RespiGam™ was licensed following recommendations of the December 14, 1995 meeting of the Blood Products Advisory Committee. At this meeting PREVENT and the NIAID trial were reviewed in detail.

PREVENT was the pivotal trial supporting RespiGam™ licensure. Randomization into PREVENT occurred between November, 1994 and December, 1994. PREVENT was a randomized, double blind, placebo-controlled study performed in children ≤ 24 months of age with BPD or prematurity (≤ 35 weeks gestation) and who were less than six months of age at enrollment. The dose of RSV IVIG was 750 mg/kg (approximately 15 mL/kg) every month from November through April (six months). 510 patients were studied and the results are shown in Tables 1 and 2.

Table 1. Summary of PREVENT Results

Endpoint	placebo n = 260	RSV IVIG n = 250	% reduction
incidence of RSV hospitalization	35 (13.5%)	20 (8.0%)	41%
RSV hospital days /100 children	129	60	53%
RSV hospital days with increased oxygen	85	34	60%
RSV hospital days with moderate to severe LRI / 100 children	106	49	54%
RSV ICU days / 100 children	50	28	44%
Days of RSV mech vent/100 children	20	18	10%

Table 2. PREVENT Results for Hospitalized Patients

Number hospitalized	placebo, n = 35	RSV IVIG, n = 20
Hospital days/hospitalized patient	335/35 or 9.6 days	150/20 or 7.5 days
Hospital days with increased oxygen/ hospitalized patient	221/35 or 6.3 days	85/20 or 4.3 days
Hospital days with mod to severe LRI/hospitalized patient	276/35 or 7.9 days	123/20 or 6.2 days
ICU days/ hospitalized patient	130/35 or 3.7 days	70/20 or 3.5 days
Days of mechanical ventilation / hospitalized patient	52/35 or 1.5 days	46/20 or 2.3 days

The primary endpoint was the reduction of the incidence of RSV hospitalization ($p = 0.047$). Of the above endpoints, the only one not associated with a p value < 0.05 was the reduction in total intensive care unit days and days of RSV mechanical ventilation.

Another endpoint was the incidence of any hospitalization due to respiratory illness ("respiratory hospitalization")--this incidence was 27% in the placebo group and 16% in the RSV IVIG group ($p = 0.005$). The total days of hospitalization for respiratory illness per 100 children was 317 days for the placebo group and 170 days for the RSV IVIG group ($p = 0.005$).

Subset analyses were by gender, categorical age (< or > 6 months at entry) and diagnosis. The largest reductions were seen in children > 6 months of age, all of whom had BPD. The smallest reduction was seen among children age < 6 months. PREVENT showed a similar hospitalization rate between the two trial arms among children < 6 months of age at enrollment.

Comment: A phase 4 commitment was to study safety and efficacy in infants < 6 months of age. The sponsor began a three year study of RSV-IVIG in these infants--a nonrandomized registry format. The study will begin its third year of enrollment this fall.

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[8] PREVENT Study Group. Reduction of Respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics. 1997; 99:93-99.

The second phase 3 study used to support the safety and efficacy of RespiGam was the NIAID Study. The NIAID study was a single blind trial that compared no drug to RSV IVIG (same dose as PREVENT) in 274 patients with BPD, congenital heart disease, or premature birth. Compared to control children, children randomized to RSV IVIG showed a 57% ($p = 0.029$) reduction in the incidence of RSV hospitalization, a 59% ($p = 0.030$) reduction in total days of RSV hospitalization per 100 children, a 97% ($p = 0.049$) reduction in RSV ICU days per 100 children and 100% reduction in mechanical ventilation per 100 children. One of the major safety findings of the NIAID study was an excessive number of deaths among infants who received RespiGam™ and who had congenital heart disease. There was a total of six deaths in the trial with all deaths among patients receiving RespiGam™. Five of these six deaths occurred in infants with congenital heart disease. Three of these five fatalities were directly related to the performance of heart surgery. This experience lead to the Cardiac Study (a single blind, non-placebo controlled study in 429 children with congenital heart disease).

Comment: The NIAID study was reviewed in detail at the December 2, 1993 meeting of the Blood Products Advisory Committee. At this meeting it was pointed out that the trial conduct was flawed (unblinded, local randomization at a major site) and the Committee recommended conduct of another study (the PREVENT study).

The Cardiac trial was a multi-center, randomized, non-placebo controlled, single-blind study conducted in 429 children with congenital heart disease of less than 48 months of age at enrollment. A 31% reduction in the primary endpoint (RSV hospitalization) was noted in the treatment group compared to the control group ($p = 0.164$). Not statistically significant reductions were observed in the treatment group in the incidence of RSV ICU stay, RSV-associated mechanical ventilation, and supplemental oxygen use. Twenty six children died (13 in each group). Adverse events were more severe in the RespiGam™ group (64 children had severe AE compared to 44 control group children). The difference was attributable to severe or life-threatening events associated with cardiac surgery in a subgroup of children with right to left cardiac shunts--severe AE were observed in 22 of 78 (28%) of these RespiGam™ children and 4 of 47 (9%) of the corresponding control children. None of the severe AE were considered to be related to RespiGam™.

Comment: The NIAID trial and the Cardiac trial did not demonstrate efficacy in infants with congenital heart disease. It has been speculated that the volume load associated with RespiGam™ infusion may have contributed to the AE. However, infants with congenital heart disease, and especially those with right to left shunts, appear to experience morbidity and mortality that is strongly tied to their underlying cardiac condition such that RSV disease assumes much less importance in their clinical outcomes. Consequently, demonstrating efficacy in this group of infants may require novel clinical trial designs. However, the data do not suggest a detrimental effect of passive immunotherapy upon the morbidity or mortality experienced by infants with congenital heart disease. MEDI-493 has not been studied in infants with congenital heart disease. There is no reason to think that MEDI-493 would be harmful to infants with congenital heart disease (including those with right to left shunts). Consequently, it is advisable to request a follow-up study of MEDI-493 use in these infants. Because no safety concerns have arisen from MEDI-493 use, it is reasonable to utilize a registry format for collection of safety concerns from infants who are administered MEDI-493 and those who are assigned not to receive MEDI-493.

The experience with RespiGam™ suggests that immunoprophylaxis of severe RSV disease is safe and effective. Since RespiGam™ is a polyimmunoglobulin it is conceivable that some of the benefit may have been attributable to non-RSV immunoglobulin. The effect of this "carrier" immunoglobulin should not be seen in MEDI-493 trials.

Two monoclonal antibodies have failed to demonstrate efficacy in phase 3 studies. One of the antibodies was an IgA product applied to the nasal mucosa. A large phase 3 study showed no difference in RSV hospitalization rates between the IgA-treated group and a placebo group. There were no safety concerns raised in this study.

The other study was another monoclonal antibody to RSV F protein which also failed to show a difference

in RSV hospitalization rates in a phase 3 study. However, the conduct of this trial was marginal with nearly one-third of the subjects failing to comply with the regimen. We do not have a complete study report from the sponsor but the summary report notes no remarkable adverse events.

2.0.0 PRECLINICAL TESTING:

Comment: The following is a brief reiteration of the sponsor's description of the preclinical testing data. These data will be explored in detail by the pharmacology/toxicology reviewer. However, they have implications for clinical assessment that are reiterated here.

2.1.0 MEDI-493 binding properties:

The sponsor notes that MEDI-493 binds to the RSV F protein with a Kd of approximately 1 nM which is similar to that of the isotype matched chimeric version of the parent monoclonal antibody. The sponsor also notes that MEDI-493 neutralizes both A and B laboratory subtypes and has been shown to neutralize 57 separate clinical isolates of both A and B subtypes.

Comment: It is of theoretical concern that not all subtypes of RSV will be sensitive to MEDI-493. Potentially, MEDI-493 might "select out" certain nonneutralized subtypes such that these become more prevalent. The selection of "escape mutants" or nonneutralized subtypes should be considered in phase 4 discussions.

2.2.0 Preclinical models of RSV:

The sponsor has performed several experiments utilizing the cotton rat model of RSV disease. In general, RSV is inoculated into the nares of the animals and the resulting viral load and pathology noted in the lungs and upper airways. Infected animals develop bronchiolitis and focal pneumonia. These studies showed that MEDI-493 was effective in both prophylaxis and treatment of RSV pulmonary infection. The sponsor felt that the prophylactic MEDI-493 blood level which resulted in a pulmonary viral titer reduction of at least 100 fold compared to placebo was probably an "effective" blood level--this level was found to be > 30 to 40 mcg/mL at the time of viral challenge. Additional studies showed the MEDI-493 did not induce enhancement of infection or subsequent pathology upon primary or secondary infection with RSV, and that MEDI-493 administration did not preclude the development of innate immunity to RSV.

Comment: It would have been useful to know the blood level that protected against bronchiolitis rather than just the blood level that produced a 100 fold decrease in lung RSV viral titer. However, in these experiments no quantitative correlation of pathology to blood level was performed.

2.2.1 Preclinical safety studies:

The sponsor has performed safety studies in monkeys, rabbits, and cotton rats. Additionally, *in vitro* human tissue cross reactivity have been performed. The following points summarize the findings:

1. IV infusion of MEDI-493 at doses of 10 and 30 mg/kg into monkeys showed no clinical or histopathological toxicity.

2. Rabbits given IM and SC injections of MEDI-493 at doses of 15 and 50 mg/kg showed no clinical or histopathological toxicity.

3. Human tissue cross reactivity studies were performed using 30 human adult and neonatal tissues with no positive staining.

Comment: The preclinical testing of MEDI-493 was somewhat limited by the development of antibodies in the experimental animals. The preclinical data show that a single dose 3 X the recommended clinical dose produced no toxicity.

3.0.0 SUPPORTIVE CLINICAL STUDIES:

The sponsor provides a detailed study report and SAS data sets for a single phase 3 study (IMpact-RSV trial). This study provides the bulk of safety and efficacy data for MEDI-493 and is reviewed in greatest detail. The sponsor also provides study reports for several supportive phase 1 and phase 2 studies. The supportive studies are summarized below and followed by a detailed clinical review of IMpact-RSV.

Some of the supportive studies utilized early manufacturing versions of MEDI 493 (a liquid formulation) and examined both the IV and IM administration routes. The supportive studies MEDI-493 was initially manufactured in a liquid formulation and tested with IV administration (Study numbers MI-RSV-9401 parts A, B, and C and Study numbers MI-CP005, MI-CP009, MI-CP013 and MI-CP026). Subsequently a study was performed with IV administration of a lyophilized preparation (Study number MI-CP017) and IM administration of the lyophilized product (MI-CP007, MI-CP011, MI-CP012 and IMpact-RSV).

There was a total of 14 clinical studies performed with MEDI-493 between 1994 and 1997. There were five studies performed in adult volunteers (MEDI-493 n = 38), four prophylaxis studies conducted in pediatric subjects (MEDI-493 n = 1169), and five treatment studies conducted in both adult and pediatric patients (MEDI-493 n = 75). All studies are summarized in Table 3.

Table 3. MEDI-493 Clinical Studies

Type of Study	Study number	Number of subjects receiving study agents		
		MEDI-493 (dose)		Placebo
Adult Volunteer	MI-RSV-MAb9401a	4	1 mg/kg IV	0
	MI-RSV-MAb9401b	12	3, 10 or 15 mg/kg IV	0
	MI-RSV-Mab9401c	12	3, 10 or 15 mg/kg IV	0
	MI-CP017	6	15 mg/kg IV	0
	MI-CP007	4	3 mg/kg IM	0
Prophylaxis	MI-CP011*	65	5, 10 or 15 mg/kg IM	0
	MI-CP012*	59	5 or 15 mg/kg IM	0
	MI-CP005	42	3, 10 or 15 mg/kg IV	20
	MI-CP018*	1002	15 mg/kg IM	500
Treatment	MI-CP034	15	15 mg/kg IV	0
	MI-CP004	6	15 mg/kg IV	0
	MI-CP026	17	15 mg/kg IV	18
	MI-CP013	7	5 or 15 mg/kg IV	7
	MI-CP009	30	5 or 15 mg/kg IV	29
Total	All Studies	1,281		574

*denotes those clinical studies utilizing the formulation and dose under review for licensure

A total of 1,099 pediatric subjects have received MEDI-493 using the formulation, dose and route of administration under licensure review.

Comment: Some of the above studies examined the use of MEDI-493 in the treatment of established RSV disease. These studies are not combined with the prophylaxis studies in reviewing the safety of MEDI-493 because of the large difference in the patient populations. However, the treatment studies are included in this review. The sponsor is not seeking an indication for the use of MEDI-493 in the treatment of established RSV disease.

The sponsor does not have clinical data assessing the effect of MEDI-493 doses greater than 15 mg/kg (the recommended dose). The sponsor has a study in progress examining an IV dose of MEDI-493 at 30 mg/kg. Considering that the preclinical data demonstrated no toxicity at higher doses it is unlikely that higher doses would be unsafe.

It is also notable that, exclusive of the phase 3 study, only 97 pediatric patients received MEDI-493 in the formulation, dose and route of administration under licensure review and these two studies were open label, non-placebo controlled studies. Consequently, the only study assessing the efficacy of MEDI-493 is the phase 3 study.

Note that the sponsor includes one additional patient in study MI-CP012 in some of the summary statements regarding study agent exposure. This patient is deleted from Table 3 because the agent was not administered.

3.1.0 Study number MI-RSV-9401 (liquid formulation, IV):

This study was the initial introduction of MEDI-493 into humans and consisted of three parts--a,b,c. The major conclusion from these studies was that MEDI-493 was well tolerated when administered at doses through 15 mg/kg for three administrations and that the half life following IV administration of the liquid formulation was approximately 17 days. Twenty of the 28 subjects showed no antibodies to 493 in the anti-MEDI-493 enzyme immunoassay (ELISA). Eight subjects showed low level, transient responses.

3.1.1 Part A:

This was an open label study in 4 adult volunteers using a single IV dose of 493 at 1 mg/kg infused over 15 minutes. This was the initial clinical protocol and was placed on hold briefly because of inadequate viral clearance in the manufacturing. The sponsor promptly added an additional viral clearance step and the protocol was allowed to proceed by mid December, 1994. Following a single IV dose of 493 at 1 mg/kg in normal adults, the half life for elimination was an average of 17 (± 6.9) days and the volume of distribution was 70 mL/kg. Patient number 2 in this trial had a number of adverse events (such as headache, nausea, etc), several of which preceded drug infusion. Otherwise, the drug was well tolerated.

3.1.2 Part B:

This was an open label study in 12 adult volunteers of 3 mg/kg, 10 mg/kg or 15 mg/kg given IV--four subjects per dose with a single dose administered. The study was completed in July, 1995. Following a single IV dose of 493 at 3 mg/kg, 10 mg/kg or 15 mg/kg the PK were virtually the same as in Part A. MEDI-493 was tolerated well.

3.1.3 Part C:

An open label study in 12 adult volunteers of 3 mg/kg, 10 mg/kg or 15 mg/kg given IV on days 0 and 30--ie., a repeat dosing study. The study was modified to administer a third dose to the 15 mg/kg group. Hence, the 15 mg/kg cohort received a total of 3 doses. This study was completed in October, 1995. MEDI-493 was tolerated well. There was no statistically significant differences in either Cmax or the half life of elimination following the first and second doses at 3 or 10 mg/kg and following the first, second and third dose at 15 mg/kg. The mean half life after the third dose at 15 mg/kg was 20 (± 8) days.

3.2.0 Study number MI-CP007 (lyophilized formulation, IM):

An open label study in which four adult volunteers received lyophilized MEDI-493 IM at a dose of 3 mg/kg every 30 days X 2. The study was completed in February, 1996. MEDI-493 was tolerated well. Peak serum levels were attained at five days after injection and average serum levels were similar to levels achieved following IV administration. The major conclusion was that the half life following IM administration of the lyophilized product was that the half life following IM administration was 21 (± 8) days (first injection) and 13 (±3) days (second injection). Two subjects developed transient, low level antibodies to MEDI-493 (anti-idiotypic). These were not detectable by 4 or 44 days post dose.

3.3.0 Study number MI-CP017 ((lyophilized formulation, IV):

An open label study in which six adult volunteers received a single dose of the lyophilized MEDI-493 at 15

mg/kg. The study was completed in June, 1996. MEDI-493 was tolerated well. No subjects developed antibodies to MEDI-493. The mean half life of elimination was 16 days with a range of 8 to 30 days.

Comment: Overall the five studies in adult volunteers showed that the half life of elimination of MEDI-493 was approximately 17-20 days when administered either IV or IM and that MEDI-493 was safe through at least three monthly injections (with the upper most test dose of 15 mg/kg). There were no safety signals in the adult volunteer studies.

3.4.0 Study number MI-CP005 (liquid formulation, IV):

This was a randomized, double blind, placebo controlled, multicenter, phase 1/2 prophylaxis study conducted among infants and children in the USA during the 1995-1996 RSV season. Follow-up has been completed through the 1996-1997 RSV season. The study was entitled "A phase 1/2 rising, repeat dose, safety, tolerance and pharmacokinetic study of MEDI-493, a humanized monoclonal antibody to RSV, conducted in premature infants and infants with bronchopulmonary dysplasia."

A total of 62 infants were dosed during the 1995-1996 RSV season in the USA and follow-up was continued through the 1996-1997 RSV season. The eligible patients were the same as those studied in the phase 3 study.

The doses were administered monthly, IV for five months and the following subjects were enrolled and infused (Tables 4 and 5):

Table 4. Study MI-CP005 Enrollment

Number of subjects	Dose
10	3 mg/kg
10	10 mg/kg
22	15 mg/kg
20	0 (placebo)

Table 5. Study MI-CP005 Infusion Record

Number of subjects	Infusions received
1	0
1	1
2	2
18	3
22	4
18	5

Comment: Several of the patients did not receive all five injections because they were enrolled late in the RSV season.

Overall, the AE profile of the two treatment groups were similar and there were no safety signals from this study. There was one death--in the placebo group.

Pharmacokinetic analyses showed that the mean nadir serum level after the first infusion was:

	3 mg/kg	10 mg/kg	15 mg/kg
level	6.8 mcg/mL	36.1 mcg/mL	60.6 mcg/mL

and the mean nadir serum level after the fourth infusion was:

	3 mg/kg	10 mg/kg	15 mg/kg
level	17.7 mcg/mL	57.1 mcg/mL	96.9 mcg/ml

Anti-MEDI-493 antibodies developed in five infants:

Three infants assigned to placebo had transient (returned to baseline within 30 days after the maximum level achieved) low level (less than 1:80) antibodies.

Two infants assigned to 15 mg/kg had transient elevations of antibodies--one had a maximum titer of 1:40 and returned to baseline within 60 days, one had a titer of 1:320 by day 45 which had returned to baseline by study day 60.

Efficacy was uninterpretable since only four patients were hospitalized for RSV illness (two in placebo group, two in 3 mg/kg MEDI-493 group). Ten patients had respiratory symptoms associated with positive RSV antigens. Sixty of the 62 infants were followed during the 1996-1997 RSV season. Two of these infants had RSV hospitalizations (one in placebo group and one in 3 mg/kg group). Neither infant required mechanical ventilation. Clinical outcomes are shown in Table 6.

Table 6. Study MI-CP005 Outcomes

Outcome, Number with:	Placebo n = 20	MEDI-493		
		3 mg/kg n = 10	10 mg/kg n = 10	15 mg/kg n = 22
any respiratory infection	17	9	4	22
RSV illness	4	3	1	2
Non-RSV illness	13	6	3	20
Otitis	14	6	10	6

Comment: Based upon the cotton rat studies which showed a 99% decrease in the pulmonary RSV titer when a serum level of 40 mcg/mL was maintained, the sponsor felt that a dose of 15 mg/kg was the most appropriate dose for subsequent prophylaxis studies.

3.5.0 Study numbers MI-CP011 (USA, Panama, Costa Rica) and MI-CP012 (Australia, New Zealand, South Africa) (lyophilized formulation, IM):

These two phase 1/2 prophylaxis studies were virtually identical except one (MI-CP011) was conducted in the northern hemisphere and the other (MI-CP012) was conducted in the southern hemisphere. The CP011 study was conducted during the last part of the northern hemisphere 1995-1996 RSV season (started in March, 1996). The CP012 study was conducted during the 1996 southern hemisphere RSV season. These studies were open label prophylaxis studies conducted in the same target population as studied in the phase 3 study. The CP-011 study consisted of three treatment arms--MEDI-493 at doses of 3, 10 or 15 mg/kg administered IM, monthly X 5. The CP-012 study consisted of two treatment arms--MEDI-493 at doses of 5 or 15 mg/kg. Sixty-five subjects were studied in CP011 and 60 subjects were studied in CP012. One subject was found to be ineligible for CP012 and was not administered the study agent. The dose groups are shown below, along with the number of anticipated injections (Table 7).

Table 7. Study MI-CP011/MI-CP012 Enrollment

Study	Number of subjects	Dose	Number of injections planned
MI-CP011	11	5 mg/kg	2
	6	10 mg/kg	2
	48	15 mg/kg	2 (in 19 subjects); 5 (in 29 subjects)
MI-CP012	11*	5 mg/kg	5
	49	15 mg/kg	4 to 5

*one patient did not receive the study agent

CP011: Of the sixty five subjects enrolled, 62 completed the 30 day follow-up after the last dose. Of the missing three subjects, two died and one was lost to follow-up. All subjects in the 5 and 10 mg/kg dose groups received their two injections. Of the 48 subjects in the 15 mg/kg group, one patient received only four injections and eight received only one injection (19 patients were eligible for two injections; 29 were eligible for five injections). Overall, MEDI-493 was tolerated well. Only two of the 62 subjects were hospitalized for RSV infections (both in the 5 mg/kg dose group). Two subjects died in the trial, both of causes apparently unrelated to MEDI-493 (SIDS and adenovirus pneumonia). The mean trough (30 days post dose) MEDI-493 levels achieved after the first injection were 11 mcg/mL in 5 mg/kg subjects, 48 mcg/mL in 10 mg/kg subjects and 49 mg/kg in 15 mg/kg subjects. The half life determined from the first and second injections ranged from 18-32 days. Ten subjects developed antibodies to MEDI-493 (titers of 1:10 to 1:40).

CP012: Of the 60 subjects enrolled, four did not complete the 30 day follow-up (one found to be ineligible to participate and did not receive the study agent, one subject died and two were lost to follow-up). Eight subjects in the 5 mg/kg group received all 5 injections. In the 15 mg/kg group, one patient received one injection, two received two injections, 11 received four injections and 35 received five injections. Overall, MEDI-493 was tolerated well. However, one patient in the 15 mg/kg group developed a moderate elevation in the SGPT that was judged to be possibly related to MEDI-493. This elevation had returned to normal by the time of the scheduled subsequent injection. Pharmacokinetic findings paralleled those from CP011. Thirteen subjects developed anti-MEDI-493 antibodies (1:10 to 1:40). Only one patient (5 mg/kg group) was hospitalized for RSV.

Comment: The sponsor's selection of the 15 mg/kg dose is largely based upon preclinical models of RSV lung infection and the pharmacokinetics obtained in the phase 1/2 studies. Obtaining dose responses based upon RSV hospitalization rates or some other clinical parameter would have been desirable but would probably have been very difficult because of the low incidence of hospitalization. The cotton rat model is a fairly well accepted model of RSV infection. Consequently, the sponsor's approach in dose selection seems reasonable. However, it would have been desirable to study even higher doses from a safety perspective.

Addendum: On March 18, 1998 the sponsor submitted the study report for a PK study of 15 mg/kg and 30 mg/kg, IV as a single dose in healthy volunteers. The most remarkable finding was that there were approximately 30% allergic reactions (rash, pruritus, chest tightness) among the 12 subjects participating. The sponsor felt the allergic reactions might be related to immune complexes, so the study was repeated in 12 more subjects but this time the doses were reconstituted with sterile water (rather than 5% dextrose and an in-line filter was utilized. None of the patients in this second part of the study experienced allergic reactions. MEDI-493 was well tolerated intravenously when it was reconstituted with sterile water and an in-line filter utilized. MEDI-493 for prophylactic (IM) use is to be reconstituted with sterile water.

3.6.0 Study number MI-CP009 (liquid formulation, IV):

This was a randomized, double blind, placebo controlled study of a single dose of MEDI-493 in the treatment of previously healthy children hospitalized with RSV. The doses studied were 0, 5 or 15 mg/kg MEDI-493 (Table 8). Nine USA sites and one Panama site participated in this study which was conducted late in the 1995-1996 RSV season (beginning in February, 1996). Sixty subjects were enrolled (all patients could not be utilizing mechanical ventilation). One subject did not receive the MEDI-493 15 mg/kg placebo dose.

Table 8. Study MI-CP009 Enrollment

Number of subjects	Dose
8	5 mg/kg Placebo
22*	15 mg/kg Placebo
8	5 mg/kg MEDI-493
22	15 mg/kg MEDI-493

*one patient did not receive the study agent

Adverse events (AE) were similar in the groups. Eight AE in five subjects were judged by the blinded investigators as possibly, probably, or definitely related to study agent. These events were fever and tachycardia, progressive respiratory failure leading to mechanical ventilation and leukocytosis, all in placebo patients; and mild generalized rash with fever and tachycardia with onset the day of infusion and respiratory failure with *H. influenzae* pneumonia, all in MEDI-493 subjects. There was one death, in the placebo group Laboratory AE were balanced between placebo and treatment groups.

There was a 21% greater number of hospital days per 100 children in the 5 mg/kg MEDI-493 group compared to the placebo group (less than the standard error of the estimated number of hospitalization days). The 15 mg/kg MEDI-493 group compared to the placebo group had 41% fewer hospital days per 100 children (276 vs. 466), admission to ICU (4.5% vs. 19%), days of ICU per 100 children (18 vs. 113), days of mechanical ventilation per 100 children (13 vs. 43), and days of supplemental oxygen per 100 children (218 vs 348). These subjects will be followed up for one year (through the next RSV season).

Comment: This study suggests no harmful effect of MEDI-493 when administered as a single IV dose to subjects with established RSV infection. The trial was not designed to determine efficacy and no efficacy conclusions can be drawn from the data.

3.7.0 Study number MI-CP013 (liquid formulation, IV):

This was a randomized, double blind, placebo controlled phase 1/2 study of a single dose of MEDI-493 in the treatment of previously healthy children hospitalized with RSV in Australia, New Zealand and South Africa. The study was comparable to Study number MI-CP009. The study began in July, 1996 and enrolled 14 subjects (Table 9):

Table 9. Study MI-CP013 Enrollment

Number of Subjects	Dose
5	5 mg/kg Placebo
2	15 mg/kg Placebo
5	5 mg/kg MEDI-493
2	15 mg/kg MEDI-493

Adverse events were similar among the groups and balanced between placebo and MEDI-493. One AE (fever) was judged by the investigator as possibly, probably, or definitely related to the study agent (was MEDI-493). There were no deaths in the study. No differences in duration of hospitalization or use of mechanical ventilation was noted. These subjects will be followed up for one year (through the next RSV season).

Comment: These two studies suggest that MEDI-493 may be investigated without undue initial safety concerns as a treatment for established RSV infection. These studies are on-going.

3.8.0 Study number MI-CP026 (liquid formulation, IV):

This was a randomized, double blind, placebo controlled, phase 2 study of the effect of a single dose of MEDI-493 in the treatment of RSV infection among subjects hospitalized with RSV who were requiring mechanical ventilation. The main objective of the study was to examine the tracheal aspirate content of RSV, comparing MEDI-493 patients to placebo patients. Thirty-five subjects received either placebo (18 subjects) or 15 mg/kg MEDI-493 (17 subjects). The study was conducted in the USA during the 1996-1997 RSV season. Only one of the enrollees had BPD, the remainder had a history of prematurity. The eligibility criteria were not the same as those for the phase 3 study--subjects had to be undergoing mechanical ventilation and be under 24 months of age (ie., it could include previously healthy patients).

Treatment with 15 mg/kg MEDI-493 was associated with a significant reduction in the titer of RSV in tracheal secretions. For patients who had both a day 0 and day 1 result (18 placebo patients and 17 MEDI-

493 patients), the mean log_{10} pfu/mL in the placebo group declined from 4.7 on day 0 to 4.1 on day 1, and in the MEDI-493 group from 4.8 on day 0 to 3.1 on day 1. The mean decline in log pfu from day 0 to day 1 was 0.6 in the placebo group and 1.7 in the MEDI-493 group, which was a 1.1 log greater decline in the treated patients. There was no difference in the two groups with respect to the titer of RSV recovered from nasal aspirates.

No AE were related to the study agents. There was one death from progressive respiratory failure (placebo patient). There were no difference in markers of severity of illness (duration of hospitalization, duration of mechanical ventilation or duration of supplemental oxygen use).

Comment: The sponsor cites this study as evidence of MEDI-493 bioactivity within the lungs. This study should be regarded as solely supportive of MEDI-493 effects because there is much variability in measuring tracheal aspirate fluid and expressing it quantitatively (dilution factors, time of collection factors). However, the study was randomized and double blind and the results are consistent with some bioactivity of MEDI-493.

3.9.0 Study number MI-CP004 (liquid formulation, IV):

This was an open label, single center, single dose pharmacokinetic study of the effects of MEDI-493 in six patients who had undergone bone marrow or stem cell transplantation. This phase 1 study enrolled six patients between the ages of 2 and 60 years who had undergone transplantation within the past six months. All patients received 15 mg/kg MEDI-493, IV. The mean serum half life of MEDI-493 was 22 days (range 10 - 57 days). No unexpected AE were seen in this study.

Comment: This is a relatively unremarkable study, which largely confirms the previously noted pharmacokinetic findings.

3.10.0 Study number MI-CP034: (liquid formulation, IV):

This was an open label, single center, single dose study of the effect of MEDI-493 in the treatment of RSV infection among hospitalized bone marrow transplant patients. The MEDI-493 dose was 15 mg/kg. Fifteen subjects were treated. THE RESULTS OF THIS TRIAL ARE PENDING.

4.0.0 ONGOING STUDIES:

The sponsor has several ongoing studies. The protocols for these studies have been submitted to the IND and are active. All results from these studies are pending (Table 10).

Table 10. Ongoing Clinical Studies

Study number	Objective	Design
MI-CP0036	safety and immunogenicity of MEDI-493 given during a second RSV season	open label, multicenter study of high risk subjects from the phase 3 study; subjects who received either MEDI-493 or placebo in the phase 3 study will receive MEDI-493 (15 mg/kg, X 5 injections); At least 60 subjects will be enrolled, with at least 15 of these being placebo subjects from the phase 3 study; investigators remain blinded to treatment assignment from phase 3 study;
MI-CP035	safety, pharmacokinetics of a single IV dose of MEDI-493 in adult volunteers	open label, phase 1 study in 12 subjects; MEDI-493 dose is 15 or 30 mg/kg

Comment: The supportive studies of MEDI-493 provide no safety signals of notable concern. It is remarkable that the choice of dose is based upon PK results from these studies and preclinical models. Only two relatively small studies (both open label, noncontrolled) examined the proposed dose to be recommended for licensure. Consequently, the phase 3 study (MI-CO018) provides all efficacy data and almost all safety data.

5.0.0 PHASE 3 STUDY DESIGN:

The phase 3 study was entitled "A pivotal phase 3 study of MEDI-493, a humanized respiratory syncytial virus monoclonal antibody for the prophylaxis of severe RSV disease in premature infants and infants with bronchopulmonary dysplasia (BPD)." The sponsor refers to this study as "IMpact-RSV"--IM RSV prophylaxis study. This study was presented to the FDA prior to its initiation and relatively minor suggestions for alteration were made.

5.1.0 Overview:

The study was conducted in the northern hemisphere (USA, Canada, Great Britain) during the 1996-1997 RSV season. The study randomized infants and children at high risk for severe RSV disease to either MEDI-493 (15 mg/kg IM) or placebo monthly for up to five injections. Subjects were randomized 2:1 (MEDI-493: placebo). The primary endpoint was a comparison of RSV hospitalization rates between the two groups. The trial was concluded when the 30 day follow-up of the last treated subject was complete.

Comment: IMpact-RSV was almost a duplicate of the PREVENT clinical trial, except for larger enrollment and 2:1 randomization. The 2:1 randomization was prompted by some concern of randomizing subjects to placebo (especially since a polyclonal gamma globulin preparation was commercially available for RSV prophylaxis).

5.2.0 Dates of trial milestones:

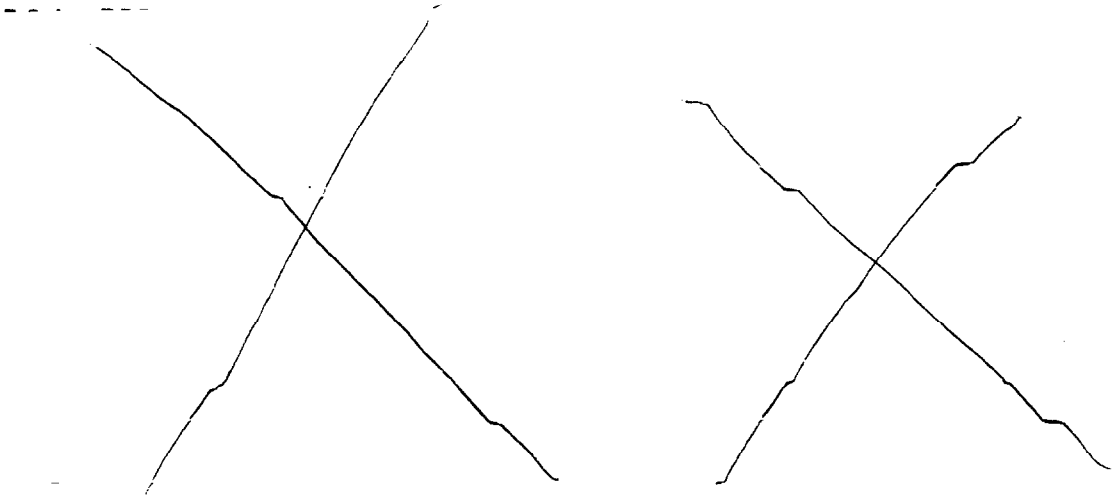
Table 11 summarizes the time of notable trial milestones.

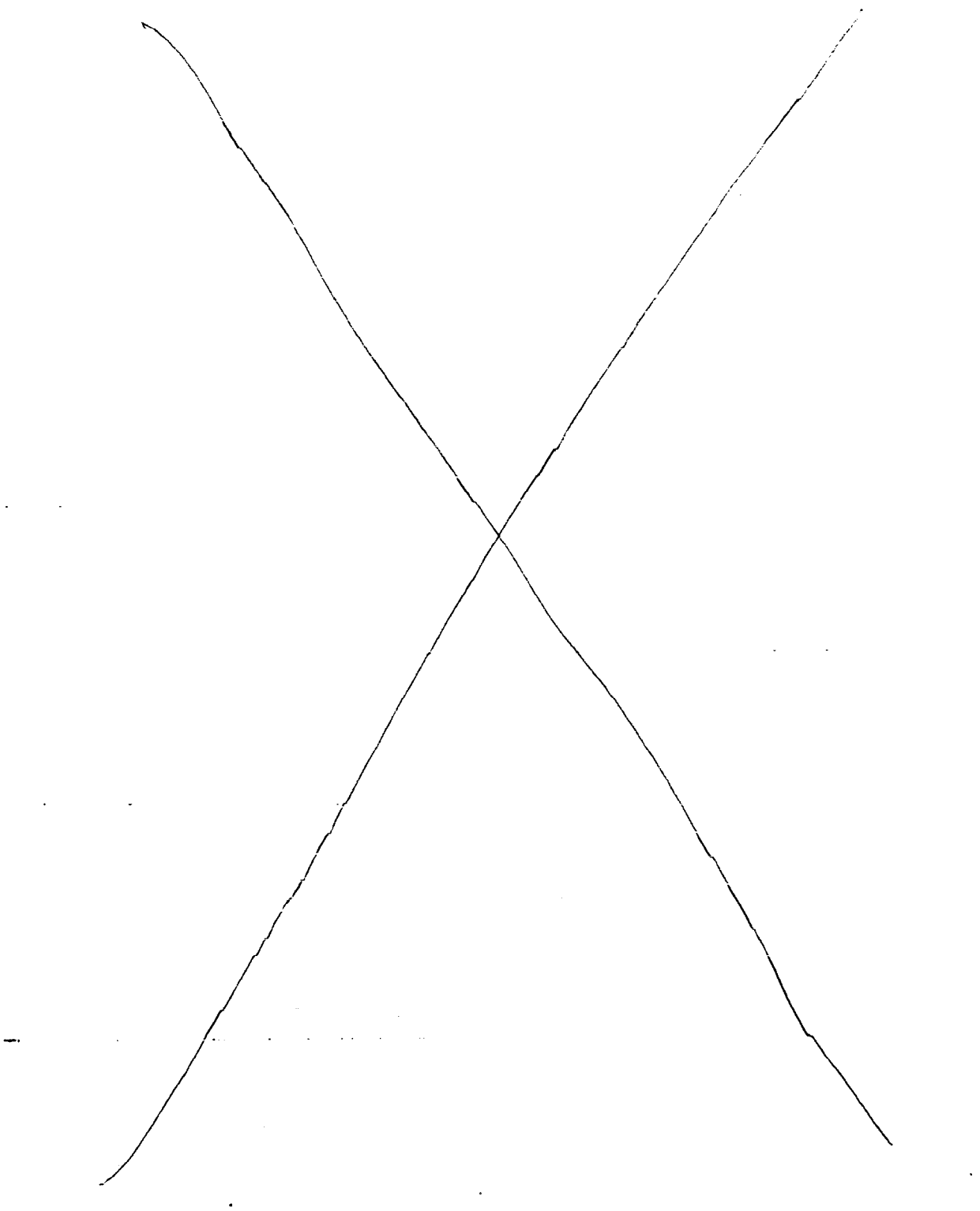
Table 11. IMpact-RSV Trial Milestone Dates

July 30, 1996	End of phase 2 meeting with CBER
November 8, 1996	Phase 3 protocol finalized
November 15, 1996	First subject enrolled/injected
February 24, 1997	DSMB teleconference review of safety data
May 12, 1997	30 day follow-up complete for last subject
July 15, 1997	Database unblinded
September 4, 1997	PreBLA meeting with CBER
December 19, 1997	BLA submitted

5.3.0 Contract Research Organizations (CRO):

The sponsor of IMpact-RSV was MedImmune, Inc. [redacted] CRO were involved in the conduct of the study. These are listed below, along with their responsibilities.





Comment: I reviewed this IND amendment with Ms. Pat Holobough of the Office of Compliance. The ERG was to remain blinded to treatment assignment and was to only propose queries ——— The final resolution of queries was the responsibility ——— We had no substantive comments following our review of this operating procedure. No definitions were altered from the clinical protocol and no new analytical plans were proposed in this amendment to the IND.

The standard operating procedures (SOP) for the DSMB were prospectively stated (in general statements within the clinical protocol and in a more explicit amendment to the IND). The DSMB was to meet only one time and was to review blinded safety and baseline demographic data once 50% of all anticipated injections had been administered. Blinded data serious adverse event (SAE) and demographic data were initially to be provided by [redacted] aison (data were presented for three groups, as X, Y, Z). If unblinding was requested, it was to proceed according to the following plan:

RSV hospitalization was not to be recorded as an AE and was not to be presented for data review.

5.4.2 MedImmune Endpoint Review Group:

The Endpoint Review Group (ERG) was described in an amendment to the IND, but no in the clinical protocol. The IND amendment was entitled, "Endpoint Verification Procedure" and described the ERG as a group charged with ensuring the accuracy of the data. The group consisted of the following individuals (all MedImmune employees):

-E. Connor, M.D.
-F. Top, M.D.
-J Balsley, M.D., Ph.D.
-D. Carlin, Ph.D.
-B. Mannion, R.N.

The ERG was to operate under an SOP which was prospectively designed and submitted with the BLA for review. According to this SOP the ERG was to perform the following with use of blinded data:

-PPD was to photocopy the CRF from all subjects reaching any primary or secondary endpoint
-as the trial was progressing, the ERG was to review the CRF and complete a query form which was to be sent back [redacted] the query form was to state "verified" or request clarification; [redacted] was to correct/answer the query and return the response to ERG; again, the ERG responded with either "verify" or query again
-at the conclusion of the trial, but prior to locking the database SAS printouts of endpoint data will be compared to [redacted] data listings and all SAE were to be cross checked against hospitalization data
-all records were to be maintained by Ms. Barbara Mannion at MedImmune

Comment: We have no information regarding the conduct of this aspect of the trial. I will request that this aspect be audited in some manner to ensure that no unblinding occurred.

5.5.0 Clinical protocol:

The clinical protocol was finalized prior to initiation of the clinical trial. There were no alterations or amendments to the clinical protocol after initiation of the trial. However, a "statistical analytical plan" was utilized as an SOP for analyzing the trial data and an "Endpoint Verification Procedure" was utilized as an SOP for verifying the accuracy of the database. Both of these SOP were submitted to the FDA after finalization of the clinical protocol and initiation of the clinical trial, but prior to unblinding of the trial database. Both SOP were reviewed by the FDA. The milestones in the clinical protocol development are summarized below (Table 12).

Comment: Note that the sponsor refers to a single protocol amendment (dated November 8, 1996). This "amendment" described certain changes to the July 16, 1996 draft protocol. These changes were incorporated into the final clinical protocol (dated November 8, 1996). There were no amendments to the final clinical protocol.

Table 12. Clinical Protocol Milestones

May 31, 1996	Submission to IND of an abstract of a proposed phase 3 clinical study
July 16, 1996	Submission to IND of the phase 3 study protocol
July 30, 1996	Protocol discussed at end of phase 2 meeting with FDA; subsequently protocol was modified
November 8, 1996	Protocol finalized
December 10, 1996	Submission to the IND of SOP for statistical analytical plan
February 12, 1997	Submission to the IND of SOP for Endpoint Verification Procedure

The following review of the clinical protocol is a review of the final version (dated November 8, 1996). The changes from the draft version of July 16, 1996 to the final version of November 8, 1996 were the following:

-a request that all sites obtain RSV cultures from patients hospitalized with RSV
-calculating patient weight and study drug volume to the nearest one-hundredth kg and mL, respectively
-adding an assay for RSV neutralizing antibody to the blood collected at baseline
-requiring that the second injection of study drug be given 25-30 days after the initial injection (the first draft allowed the injection between 25 and 35 days after the initial injection)

Comment: The FDA had recommended, following review of the draft protocol, that MedImmune try to devise a method of determining the number of RSV infections among all subjects in the trial, including those not hospitalized. MedImmune responded by saying that they could not devise a method for detecting asymptomatic or mild RSV disease.

5.5.1 Overview:

The protocol was entitled, "A pivotal phase 3 study of MEDI-493, a humanized respiratory syncytial virus monoclonal antibody, for the prophylaxis of severe RSV disease in premature infants and infants with bronchopulmonary dysplasia." Protocol number MI-CP018

The study monitor was [redacted]

The study was a randomized, double-blind, placebo-controlled, multicenter trial in which subjects were to receive monthly injections of the study agent (X 5 injections) during the northern hemisphere RSV season. Follow-up was to extend until 30 days after the last injection (Figure 1).

[redacted]

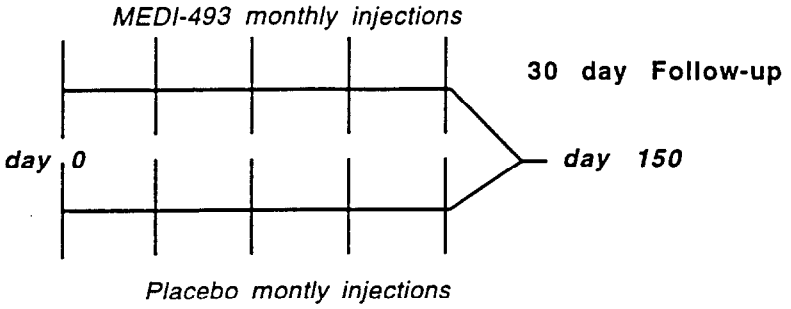


Figure 1. Study Plan

Randomization and the first injection were to be on day 0 and the last day of follow-up was day 150

Comment: As mentioned elsewhere in this review, the sponsor is studying a subset of the patients throughout the 1997-1998 RSV season.

All of the following points (objectives, eligibility criteria, endpoints, analytical plan) were explicitly stated in the trial protocol (prior to initiation of the study).

5.5.2. Objectives:

5.5.2.1 Primary objective:

"To compare the safety and efficacy of MEDI-493 to placebo when administered monthly by IM injection for the reduction of the incidence of RSV hospitalization among infants born prematurely and infants with BPD."

Comment: The primary objective is consistent with the primary endpoint.

5.5.2.2 Secondary objectives:

a. determine the effect of MEDI-493 on the following hospitalization parameters:
-total RSV hospital days
-total RSV hospital days with increased supplemental oxygen requirement
-total RSV hospital days with moderate or severe lower respiratory tract infection (LRI score ≥ 3),
-frequency and total RSV-associated ICU days
-frequency and total days of RSV-associated mechanical ventilation

b. determine the effect of MEDI-493 on the:
-incidence and total days of hospitalization for non-RSV respiratory disease and any respiratory disease and hospitalizations for any cause

c. determine the effect of MEDI-493 on the incidence of otitis media

Comment: All the objectives were also defined as endpoints in the trial with a specific delineation of how they were to be analyzed. The objectives described in the sponsor's proposed labeling include the primary objective and the following secondary objectives:
-total days of RSV hospitalization
-total days of RSV hospitalization with increased oxygen therapy
-total days of RSV hospitalization with LRI score ≥ 3
-incidence of ICU admission for RSV disease
-incidence of mechanical ventilation for RSV disease

The following results applicable to the following objectives are not included in the sponsor's proposed labeling:
-comparison of total RSV ICU days between the trial arms
-comparison of total RSV mechanical ventilation days between the trial arms
-incidence and total days of hospitalization for non-RSV respiratory disease, any respiratory disease and hospitalization for any cause
-incidence of otitis media

5.5.3 Eligibility:

Inclusion criteria:

"Children must meet at least one of the following criteria:
a. 24 months of age or younger with a diagnosis of BPD requiring medical intervention/management (oxygen, steroids, bronchodilators, diuretics) within the previous 6 months, or
b. 35 weeks gestational age or less at birth and 6 months of age or younger"

Exclusion criteria:

-hospitalization at the time of randomization (unless discharge for BPD/prematurity is anticipated within 30 days)
-mechanical ventilation (including CPAP) at time of randomization
-life expectancy < 6 months
-active RSV infection or RSV infection after June 15, 1996
-known renal impairment
-known hepatic dysfunction
-chronic seizure disorder
-congenital heart disease (except children with previous uncomplicated CHD who are currently anatomically and hemodynamically normal)
-known immunodeficiency
-known allergy to Ig products
-receipt of RespiGam™ within 3 months prior to randomization
-previous treatment with MEDI-493 or other monoclonal antibody
-receipt of RSV vaccine or other investigational agents

Comment: These criteria are virtually identical to those utilized in the pivotal phase 3 study for RespiGam™. No children with uncorrected congenital heart disease have been enrolled in MEDI-493 clinical trials. Eligibility criteria were regarded as reasonable by the FDA upon reviewing the protocol.

5.5.4 Randomization:

Coordination and daily management of the trial was to be largely performed by [redacted]). Subjects were to be randomized on the same day as the initial injection was administered. Randomization was to be into one of three groups (designated A, B, or C), two of which were MEDI-493 groups (2:1 randomization). Randomization was to be performed for the entire trial [redacted] with stratification by investigative site [redacted] was to establish a patient ID number for each subject (PID). The PID number and child's initials was to be utilized to identify each subject. At the time of enrollment/randomization, the investigator was to call [redacted] to obtain the PID number. Subsequently, the site pharmacist was to call [redacted] to obtain the drug code assignment (A, B, C) for the subject. The pharmacist was to be the only site individual aware of the drug code assignment.

Comment: Central randomization was performed with the only stratification being by investigative site. This proposal was thought to be reasonable by the FDA.

5.5.5 Study agents and their administration:

The study agents were to be administered by the clinician writing a prescription and forwarding it to the site

pharmacist. This prescription form was to contain the PID number, child's initials and child's weight (kg), date, protocol number, patient's date of birth, injection number, and total calculated amount of study drug to be injected. . The pharmacist was to prepare the appropriate amount of study agent (using the pharmacist's drug code assignment record) and forward the study agent for administration. The label on the study agent was not to contain the drug code assignment.

Both study agents were to be administered IM into either the anterolateral aspect of the thigh or the gluteal muscle. Subjects were to receive the injections in clinic, although if necessary, injections after the first visit could be given at the time of home visits.

The study drugs were to be supplied to the site pharmacists labeled with a letter code (A, B, C). MEDI-493 was to be supplied in 5 mL vials containing a lyophilized cake. Both agents were to be reconstituted with 1 mL of sterile water for injection (USP) to provide a final concentration of 100 mg/mL.

The final concentration of contents in the MEDI-493 vial were to be the following, pH 6.0:
- -MEDI-493 100 mg/mL
- -50 mM histidine
- -3.2 mM glycine
- -6% (w/v) mannitol

The final concentration of contents in the placebo vial were to be the following:
- -50 mM histidine
- -3.2 mM glycine
- -6% (w/v) mannitol
- -0.02% (v/v) Tween-80

The site investigator was to calculate the dose based upon the child's current weight, rounded to the nearest 0.01 mL.

Dose = [patient weight (kg) x 15 mg/kg] divided by the study drug concentration (100 mg/mL)

Comment: The plan for study agent administration was felt to be appropriate by FDA review.

5.5.6 Concomitant medications:

Subjects were not to receive RespiGam™ or investigational agents during the trial. There were no restrictions on the use of other medications and subjects were to receive scheduled vaccinations. All concomitant medications were to be recorded.

Comment: There was some concern that RespiGam™ might interfere with immunizations because it contained polyclonal antibodies. This concern is irrelevant for MEDI-493.

5.5.7 Evaluations:

Appendix A is a copy of the sponsor's summary table of evaluations. Three blood samples were to be collected from all patients during the trial. These samples were to be collected according to the following:
-from all subjects at baseline and prior to the fifth injection
-from all subjects at one additional time (prior to 2nd, 3rd or 4th injection), with the time of this additional blood sample being stated at randomization

The evaluations were to include the following:

-Day 0 (randomization and first injection)
- -medical history, AST, ALT, BUN, creatinine, MEDI-493 level, antibodies to MEDI-493 and blood for reserve, physical exam, lower respiratory infection (LRI) score

-Day 25-30 (second injection)

-medical history, concomitant medications, blood for MEDI-493 level, immunogenicity and reserve (selected patients), physical exam, LRI score

-Day 60 ± 5 (third injection)
-medical history, concomitant medications, blood for MEDI-493 level, immunogenicity and reserve (selected patients), physical exam

-Day 90 ± 5 (fourth injection)
-medical history, concomitant medications, blood for MEDI-493 level, immunogenicity and reserve (selected patients), physical exam

-Day 120 ± 5 (fifth injection)
-medical history, AST, ALT, BUN, creatinine, blood for MEDI-493 level, antibodies to MEDI-493 and reserve, physical exam

-Day 150 ± 7 (30 day follow-up, on or before May 15, 1997)
-medical history, physical exam

Comment: It is notable that the determination of immunogenicity of 493 will be based largely upon the blood obtained at the time of the fifth injection--not 30 days after the fifth injection.

Patients who were discontinued from the study drug were to continue to be followed every 30 days until day 150. Blood collection (for MEDI-493 levels and chemistry) were to be completed 30 days after the last dose of study drug regardless of which dose that was.

Patients were to be considered "lost to follow-up" only if no contact had been established by the time the study was complete, such that there was insufficient information to determine the primary study endpoint.

5.5.7.1 Hospitalization data collected:

Four major categories of hospitalization were to be identified and tracked:
-all hospitalizations
-respiratory hospitalizations
-non-RSV respiratory hospitalizations
-RSV hospitalizations

The decision regarding need for hospitalization was to be made by the patient's physician. Nasal swabs or wash were to be assayed for RSV antigen within 48 hours of hospitalization. Children with respiratory illness who had an initially negative RSV antigen could have the test repeated within 24 hours.

Comment: The case report forms did not track the number of times the RSV antigen test was initially performed. Only the definitive test result was captured.

The protocol noted that some children may be hospitalized for nonrespiratory illness but develop an RSV respiratory illness while in the hospital. These children were to be considered as having attained an RSV hospitalization if:
-an RSV antigen test done for evaluation of the respiratory illness is positive and their LRI score is 3 or greater and the score is at least one level higher than the last injection visit when the patient did not have an intercurrent respiratory infection.

The protocol also noted that some children may be hospitalized for non-RSV respiratory illness but develop an RSV respiratory illness while in the hospital. These children were to be considered as having attained an RSV hospitalization if:
-the patient develops a new respiratory illness or exacerbation of respiratory disease during the initial illness (but at least 48 hours after admission), and an RSV antigen is positive, and the LRI score is 3 or greater and the score is at least one level higher than the score at the last injection

visit.

Subjects who were hospitalized were to receive their regularly scheduled injections unless there was a medical contraindication.

The protocol required certain evaluations to be performed upon hospitalized patients. The initial evaluation was to proceed according to Figure 2.

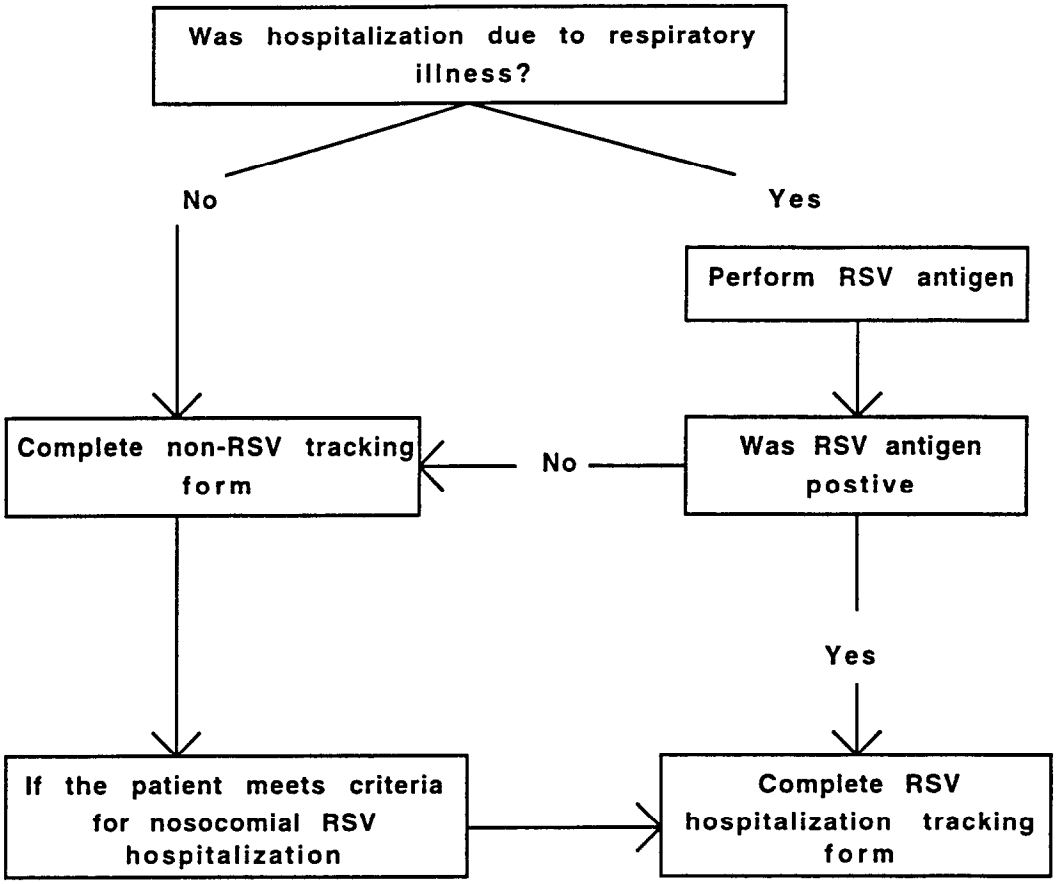


Figure 2. Hospitalization Procedures

The specific evaluations included the following:

a. For all patients hospitalized:

-day of admission: document date, time, presence/absence respiratory symptoms and signs; if admission was for respiratory illness, obtain nasal wash or nasal swab for RSV antigen (to be tested on site); history, physical exam; record use of supplemental oxygen; LRI score; the clinician was to determine whether the hospitalization was for respiratory illness or not

b. For patients hospitalized with a non-respiratory illness or a non-RSV respiratory illness:

-daily: LRI score; record any new respiratory signs/symptoms; if new respiratory illness or exacerbation of non-RSV respiratory disease develops and the LRI score is 3 or greater and the LRI score is at least one level higher than the score at the last injection visit, then a nasal wash or swab for RSV antigen was to be performed; date of discharge

c. For patients hospitalized with an RSV respiratory illness:

-day of admission: blood for MEDI-493 levels; nasal secretions cultured for RSV and isolates from positive culture frozen at -70° C for subsequent test of neutralization by MEDI-493; history , physical exam; record supplemental oxygen use; LRI score

-daily: record supplemental oxygen use; LRI score; record date of discharge for RSV illness (if a patient's hospital stay was extended for non-medical reasons or for performance of elective pre-planned surgery, the investigator was to declare the date when the patient would have been discharged for RSV illness and record this date on the CRF.

-day of hospital discharge for RSV and actual hospital discharge date (if different): record supplemental oxygen use; LRI score

d. For patients admitted to the ICU for RSV respiratory illness:

-day of ICU admission: record date, time, and reason for admission; record supplemental oxygen use; LRI score

-day of RSV-associated mechanical ventilation: record date, time of start of mechanical ventilation and reason; LRI score;

-day of ICU discharge and day of termination of mechanical ventilation: record date and time;

Comment: The data proposed to be recorded in the hospital appears appropriate and adequate.

5.5.7.2 Definitions:

The following definitions were stated in the protocol:

-RSV hospitalization: a hospitalization for a respiratory illness in which RSV antigen is detected at least once in respiratory secretions (obtained by swab or nasal wash) during the first 48 hours from the time of admission

-day of RSV hospitalization: either the day a patient with a respiratory illness was admitted and had nasal specimens collected within 48 hours of admission positive for RSV antigen, or the first day that a patient met criteria for nosocomial RSV hospitalization

-Lower Respiratory infection/illness score (LRI Score, Table 13):

Table 13. LRI Score

Score	Clinical Condition
0	No respiratory infection/illness
1	Upper respiratory tract infection/illness
2	Mild lower respiratory tract infection/illness
3	Moderate LRI
4	Severe LRI
5	Mechanical ventilation

The LRI score was to be assigned by a physician investigator, although a trained research nurse could assign the score if the physician was unavailable. The LRI score was to be an over-all reflection of the patient's total respiratory status, including any contribution of the child's underlying disease. "Thus children who have chronic lower tract disease but no acute respiratory illness may be assigned a score of 2-4, depending on severity, solely due to the existing pulmonary disease. The same child who then develops an acute respiratory infection would have a score which includes the original contribution of his/her underlying disease plus the contribution from the acute illness." The etiology of a respiratory tract

finding was not to influence the assignment of the score. The following were to apply to the scores:

-Score 0, no respiratory illness--a child with no underlying respiratory tract disease and no intercurrent respiratory illness.
-Score 1, upper respiratory tract illness--a child with no underlying lower respiratory tract disease, but who has an intercurrent upper respiratory illness. The patients generally have a normal respiratory rate. A chest radiograph will either not be medically indicated, or if done, will not reveal any evidence of lower respiratory tract illness
-Score 2, lower respiratory tract illness (mild)--a child with mild lower respiratory tract illness due to either his/her underlying condition (e.g. BPD), to an intercurrent infection or to a combination of both
-Score 3, lower respiratory tract illness (moderate)--a child with moderate lower respiratory tract illness due to either his/her underlying condition (BPD), to an intercurrent infection or to a combination of both
-Score 4, lower respiratory tract illness (severe)--a child with severe lower respiratory tract illness due to either his/her underlying condition (BPD), to an intercurrent infection or to a combination of both
-Score 5, mechanical ventilation--to be assigned to all patients who require mechanical ventilation

Comment: This scale was also utilized in the PREVENT trial. It is of uncertain prognostic significance. It is notable that the assignment among grades 2, 3 and 4 are fairly subjective (ie., mild, moderate, and severe) and the scale provides no objective criteria for making these assignments. Consequently, what one investigator might call "mild" another investigator might call "moderate." The scale provides a relatively subjective assessment of severity of illness, but, since the trial was blinded, its information should be useful.

5.5.7.3 Safety assessment:

Standard AE definitions and reporting policies were to be followed. Each AE was to be assessed by the investigator for severity, relationship to the study treatment and seriousness. A toxicity table describing characteristics to be followed in assigning severity of the AE was included in the protocol.

RSV hospitalization was not to be reported as a serious AE. RSV infection without hospitalization was to be recorded as an AE.

Comment: The safety reporting system utilized a standard format.

5.5.8 Statistical analysis:

5.5.8.1 Primary endpoint:

The primary endpoint was to be a comparison of RSV hospitalization rates. The rates were to be compared between groups using Fisher's Exact test using the "intent-to-treat" population.

5.5.8.2 Secondary endpoint:

Secondary endpoints included the following:

1. Total number of days in the hospital due to RSV illness; the total days of RSV-related hospital stay per 100 randomized children was to be compared between the study groups

2. Total hospital days with increased supplemental oxygen requirement; the proportion of patients requiring increased supplemental oxygen for RSV and the mean duration of increased supplemental oxygen during an RSV hospitalization were to be compared between study groups

3. Total hospital days with LRI Score ≥ 3; the proportion of patients with LRI scores ≥ 3 during an RSV hospitalization and the mean duration of LRI scores ≥ 3 during an RSV hospitalization will be compared between study groups

4. Incidence and duration of ICU stay; the proportion of patients requiring ICU admission for RSV and the mean duration of ICU stay for RSV will be compared between study groups

5. Incidence and duration of RSV-related mechanical ventilation; the proportion of patients requiring mechanical ventilation for RSV and the mean duration of mechanical ventilation will be compared between study groups

6. Incidence and total days of hospitalization for non-RSV respiratory hospitalization;

7. Incidence of otitis media between the two groups

Comment: The secondary endpoints are described as "secondary objectives" and follow the description of the primary endpoint in the protocol statistical section.

5.5.8.3 Additional statistical considerations:

The study was designed to test the hypothesis that MEDI-493 reduces the RSV hospitalization rate in children with prematurity ~~or~~ BPD when compared to placebo. The trial was designed assuming an RSV hospitalization rate of 13.5% in the placebo group compared to 8% in the treatment group. The estimate of 1,281 subjects allowed 80% power to show a 40% reduction in the incidence of RSV hospitalization using a 2-sided alpha of 0.05 and assuming a drop-out rate of 10%.

Comment: The estimated RSV hospitalization rates are consistent with the PREVENT data.

Randomization was to be performed centrally and stratified by center, with randomization being 2:1, MEDI-493 to placebo.

The DSMB was to be charged only with evaluation of safety; no interim evaluations of efficacy were to be done. The DSMB was to meet after approximately half of the scheduled doses of study drug have been given.

5.6.0 Statistical analysis plan:

A statistical analysis plan was submitted to the IND on December 10, 1996 and was intended to supplement the statistical description within the clinical protocol. This plan was not regarded as an amendment to the protocol. This plan is summarized below.

5.6.1 General considerations:

-all p-values were to be 2-sided
-baseline values for variables are defined as those taken closest to but prior to injection
-subjects will be considered to be on study and to have completed the study regardless of the number of injections received or visits attended if information to assess the primary endpoint is obtained through 30 days past the last scheduled injection; if no assessment of RSV hospitalization can be obtained a patient will be considered lost to follow-up
-intent-to-treat analyses were to be conducted for all primary and secondary efficacy endpoints and safety analyses; al randomized patients are to be included in these analyses; serum drug concentrations and immunogenictiy analyses were to include only those patients receiving at least one injection
-only one primary endpoint is identified and all other endpoints are identified as secondary or exploratory in nature.
-no injections were to occur after April 15, 1997; therefore any patient enrolled after December 15, 1996

was to be eligible to receive at most four injections;

5.6.2 Baseline characteristics:

Baseline characteristics were to be compared using the Wilcoxon rank sum test. The number of patients per category will be compared between groups using Fisher's Exact test.

Baseline characteristics were to include gender, race/ethnicity, multiple births, age at study entry, gestational age (≤ 32 weeks and > 32 weeks), birth weight, previous hospitalizations (no previous hospitalizations, 1 to 2, and > 2 hospitalizations), previous RSV infections, previous lower respiratory tract infections and previous incidence of BPD, LRI score at entry (LRI score ≥ 2 or LRI < 2), weight at entry, day care status, family history including number of individuals in the same household and number of smokers in the household, history of asthma, hay fever or eczema.

5.6.3 Primary endpoint:

The RSV-associated hospitalization incidence will be summarized overall for each treatment group and separately by study site, and per month.

The incidence of RSV hospitalization in either treatment groups was defined as:
number of patients with RSV hospitalization / number of patients randomized

The two groups were to be compared using Fisher's Exact test. An exact 95% confidence interval (CI) for the difference in response rates was to be calculated.

The plan noted the following:

- -each patient with an RSV hospitalization was to be counted once in the incidence analysis even if hospitalized more than once for RSV
- -in the primary analysis any patient who does not complete the study or who dies prior to experiencing the primary endpoint or end of study was to be counted in the analysis as not reaching a hospitalization endpoint. These children were to be included as having an RSV hospitalization in a secondary sensitivity analysis
- -subjects who are hospitalized with respiratory disease but do not have a test for RSV antigen were to be counted in the analysis as not reaching a hospitalization endpoint. These subjects were to be included as having an RSV hospitalization in a sensitivity analysis.
- -baseline characteristics that differ between treatment groups or are thought to have potential prognostic value were to be included in a logistic regression analysis (including sex, age, BPD and weight at study entry). The purpose of this logistic regression analysis is to refine the estimate of treatment effect obtained from Fisher's Exact test by examining treatment in the presence of these baseline differences. The plan describes the model in detail.
- -an additional estimate of RSV hospitalization will utilize Kaplan-Meier curves and groups compared using the logrank statistic

5.6.4 Secondary endpoints:

For continuous variables the two treatment groups were to be compared using the Wilcoxon Rank sum test and summarized as days per 100 randomized children. The endpoints that are discrete were to be analyzed using Fisher's Exact test.

1. Total days in hospital due to RSV

2. Total RSV hospital days with increased supplemental oxygen requirement

3. Total RSV days with LRI score ≥ 3

4. Incidence and total number of days of RSV ICU stay

5. Incidence and total days of RSV related mechanical ventilation

6. Incidence of otitis media

7. Incidence and total days of non-RSV respiratory illness hospitalization, any respiratory illness hospitalization, and hospitalizations for any cause

Comment: Unlike the protocol, the statistical plan clearly identifies these as secondary endpoints. The secondary endpoints are not ranked in any particular order.

5.6.4 Exploratory analyses:

Only if the number of events is sufficient were the following subset analyses to be performed (no p-values were to be calculated): age, gestational age, sex, weight at entry, BPD, country.

5.6.5 Safety analyses:

Standard AE analyses were proposed. Proportions were to be compared using Fisher's Exact test.

5.6.6 Definitions:

The statistical plan SOP included several definitions. These are described below:
The following definitions were stated in the SOP describing the statistical analysis:

-randomized: any patient receiving a randomization number regardless of the number of injections received

-treated: any patient receiving any amount of study drug (MEDI-493 or placebo)

-study period: the interval between day 0 through day 150. If a patient is still hospitalized at day 150, all appropriate duration parameters will be counted up to and including day 150.

-completed study: any patient experiencing an RSV hospitalization or having an endpoint assessment at day 150.

-extent of exposure: the number of injections each subject received regardless of the amount of injection;

-compliance: number of protocol visits attended

-respiratory hospitalization: a hospitalization for which the primary reason for admission was respiratory (as designated on CRF).

-non-respiratory hospitalization: a hospitalization for which the primary reason for admission was non-respiratory (as designated on CRF).

-RSV hospitalization: a respiratory hospitalization in which the RSV antigen is positive within 48 hours after admission; the following also applied: if the RSV antigen test was positive within three calendar days before a respiratory admission and the admission was caused by the illness for which the antigen test was originally done and there was no negative antigen test during the period or if the RSV antigen test was positive within three calendar days after a hospitalization for a respiratory illness and there was no negative antigen test during that period

-non-RSV respiratory hospitalization: any respiratory hospitalization, except a primary RSV hospitalization; a hospitalization which was initially not RSV but becomes a nosocomial RSV hospitalization was to be counted as a non-RSV hospitalization from the admission date until the day when nosocomial criteria were met

-hospitalization at randomization: any patient who was hospitalized at the time of randomization was not to have that hospitalization counted in the hospitalization incidence or duration analyses unless the hospitalization became a nosocomial RSV hospitalization after randomization.

-time not recorded: if the time was not obtained for any hospitalizaTion parameter in which time was to be collected, 12:00 am was to be used for admission or initiation and 11:59 pm was to be used for discharge or discontinuation.

-extended hospital stay: in cases where RSV hospitalization was to be extended, the actual discharge date and time was to be used, except if the stay was extended for social placement or preplanned surgery--in this situation the end of hospitalization was to be the date and time of RSV discharge

-mechanical ventilation for surgery: for children who were to receive mechanical ventilation (LRI = 5) only related to surgery, this specific increase in LRI was not to be used as evidence of meeting nosocomial criteria for RSV hospitalization

-otitis media: an episode of otitis media accompanied by evidence of antibiotic treatment for the event

-pharmacokinetics and immunogenicity: MEDI-493 concentrations and immunogenicity assessments were to be collected; values from samples obtained following administration of the wrong study drug or administration of insufficient (<75%) were not to be included in the descriptive summary analysis

Comment: The definition from the statistical analysis plan expand upon the protocol definitions and are not contradictory. The statistical analysis plan clarified certain aspects of the clinical protocol. It described no novel trial considerations. The plan also included detailed descriptions of the formats for summary data presentations. This analysis plan was discussed with the sponsor in a teleconference on February 20, 1997.

5.7.0 Endpoint Verification Group SOP:

On February 12, 1997 the sponsor submitted an SOP to the IND describing the ERG. The function of the ERG is described under trial committees in an earlier section of this review.

5.8.0 Case Report Forms:

The trial utilized a 60 page CRF. There was no space on the CRF permitting identification of the study agent.

Comment: The CRF are clear and easily understood.

6.0.0 PHASE 3 STUDY CONDUCT:

The first subject was enrolled into the trial on November 15, 1996 and the last day of follow-up for the final subject was completed on May 12, 1997. The DSMB met one time (teleconference) during the trial (February 24, 1997).

6.1.1 DSMB conduct:

The sponsor submits a summary letter from the Chair of the DSMB (dated August 20, 1997) delineating the actions of the DSMB. According to this letter, the DSMB reviewed blinded safety data via teleconference on February 24, 1997. The DSMB felt the three trial arms were balanced for baseline

characteristics. The board noted that there were eight cases of sepsis and that seven of these cases occurred in two of the three arms. They also noted that there were also three deaths in each of these two trial arms, while one trial arm had only one death. The board authorized Dr. DeMets to unblind the three trial arm assignments and the SOP was followed. The DSMB recommended that the trial continue.

Comment: The DSMB appears well designed and the chairman's summary statement documents that it followed all procedures appropriately.

6.1.2 Trial conduct monitoring:

Most of the clinical trial monitoring was performed by [redacted]. This included monitoring of pharmacy and drug accountability records, source data entry into CRF, site protocol adherence, and AE reporting. [redacted] audited a total of 27 sites (20% of total). The sponsor describes the specific aspects audited at these sites in the BLA submission and notes that these audits revealed only minor deviations in source documents and CRF.

Comment: The monitoring by the CRO appears reasonable. The FDA is also auditing three of the sites. The results of this audit are pending.

7.0.0 PHASE 3 STUDY PATIENT DISPOSITION:

A total of 1,502 subjects were randomized at 139 sites in the USA, the United Kingdom and Canada, between November 15 and December 13, 1996. The patient disposition is shown in Figure 3.

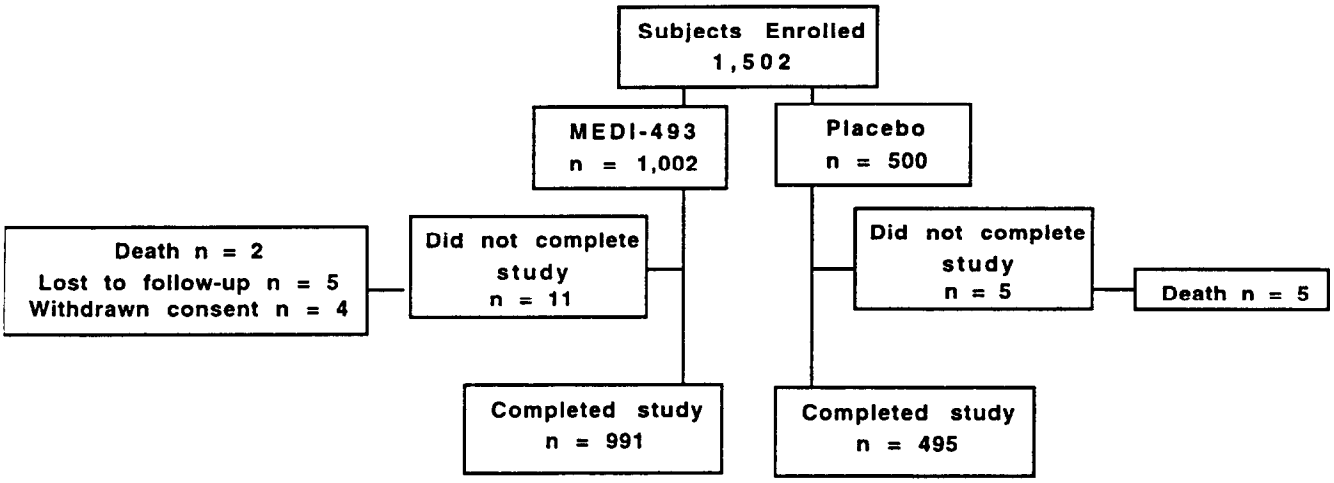


Figure 3. Patient Disposition

The number of subjects who did not complete the study is limited to those who either died before reaching the primary endpoint or who were unavailable for follow-up assessment at day 150. There were a total of nine deaths in the study, but seven of these deaths occurred among subjects prior to achieving the primary endpoint. All enrolled patients were randomized.

The enrollment by country is shown in Table 14.

Table 14. Enrollment/Randomization by Country

Country	MEDI-493, n	Placebo, n	Total, n	% of Total
USA	851	426	1,277	85
United Kingdom	83	40	123	8.2
Canada	68	34	102	6.8

There were 119 sites in the USA, 11 sites in the UK and 9 sites in Canada. From 2 to 25 subjects were randomized per site, with an average of 11 subjects per site. Eight sites randomized less than 5 subjects and 27 sites randomized 15 or more subjects.

The cause for failure to complete the study is shown in table 15.

Table 15. Subjects Who Did Not Complete the Study

Group	ID number	Study day	#injections	Reason for non-completion
MEDI-493		63	1	parent withdrew consent ("too demanding")--twins
		63	1	
		19	1	death (non-RSV pneumonia)
		61	1	lost to follow-up
		30	2	death--SIDS
		15	1	lost to follow-up
		55	3	lost to follow-up
		43	1	parent withdrew consent (employment)--twins
		43	1	
		98	3	lost to follow-up
		59	2	lost to follow-up
Placebo		86	3	death--SIDS
		28	1	death--BPD complications
		52	2	death-non-RSV pneumonia
		118	5	death--SIDS
		0	1	death-pneumococcal sepsis

None of the deaths in the MEDI-493 group was attributed to complications of the study drug. One subject in the placebo group was identified by the site investigator as having death possibly related to the study agent.

Comment: In general, the number of subjects failing to complete the study appears reasonable and balanced between the trial arms. Approximately 1/3 of enrollees were twins (multiple births). If twins were enrolled, each was randomized individually.

Excluding the nine deaths in the trial, follow-up was completed through 150 days for all but 9 patients (all 9 were in the MEDI-493 group). The number of patients with less than 150 days of follow-up is shown in Table 16.

Table 16. Follow-up < 150 Days

Group	Death	Lost contact	Withdrew consent
Placebo	5	0	0
MEDI-493	4	5	4

7.1.0 Protocol deviations:

7.1.1 Eligibility Criteria Violations:

As Table 17 shows, there were 12 patients entered into the study in violation of the study protocol. Two of these patients [redacted] were granted exemptions by the sponsor prior to randomization to allow them to enroll one day past six months of age (one randomized to MEDI-493, the other to placebo).

Table 17. Eligibility Criteria Violations

Violation	MEDI-493	Placebo	Total
BPD, but not medically managed in past 6 months	2	3	5
Premature, but age > 6 months	1	1	2
RespiGam™ within past 3 months	2	0	2
Congenital heart disease	1	0	1
RSV infection at randomization (baseline)	1	0	1
Liver dysfunction	0	1	1

7.1.2 Drug Dispensing Violations:

As Table 18 shows, there were 14 patients who had at least one drug dispensing error.

Table 18. Subjects with Drug Dispensing Errors

Randomization assignment	ID #	Error
MEDI-493	06301-4	drug-drug switch for fourth injection*
	06312-2	received placebo for third injection
	06613-3	drug-drug switch for fourth injection*
	07211-3	drug-drug switch for fourth injection*
	13614-4	received placebo for first two injections**
	21302-2	received placebo for first injection
	22401-2	drug-drug switch for second injection*
Placebo	06302-3	received MEDI-493 for fourth injection
	13601-2	received MEDI-4903 for first injection
	13615-2	received MEDI-493 for first two injections**
	25002-2	received MEDI-403 for first injection
	26506-2	received MEDI-493 for first injection
	27305-3	received MEDI-493 for first injection

*received the incorrect letter code, but correctly received MEDI-493
**was subsequently hospitalized for RSV disease

There errors resulted in seven placebo group patients receiving at least one dose of MEDI-493 and three MEDI-493 group patients receiving at least one dose of placebo. In no case were more than two incorrect study agent injections performed.

Comment: The protocol violations were minor and balanced between the trial arms.

8.0.0 Baseline Characteristics:

Table 19 presents those baseline characteristics that were prospectively identified for statistical analysis in the statistical analysis SOP for the protocol.

Table 19. Baseline Characteristics Prospectively Identified for Analysis

Characteristic		Placebo n = 500	MEDI-493 n = 1002
Sex	Male, n (%)	284 (57%)	570 (57%)
	Female, n (%)	216 (43%)	432 (43%)
Race/ethnicity	Caucasian, n (%)	287 (57%)	585 (58%)
	Black, n (%)	128 (26%)	228 (23%)
	Hispanic, n (%)	54 (11%)	110 (11%)
	Asian, n (%)	12 (2%)	21 (2%)
	Other, n (%)	19 (4%)	58 (6%)
Multiple birth	Yes, n (%)	137 (27%)	318 (32%)
Entry Age	months, mean (SE)	6 (0.2)	5.7 (0.2)
	months, range	0.2 - 23.9	0.1 - 24.1
Gestational age	weeks, mean (SE)	29 (0.1)	29 (0.1)
	weeks, range	22 - 41	22 - 40
Gestational age ≤ 32 weeks	n (%)	417 (83%)	840 (84%)
Gestational age > 32 weeks	n (%)	83 (17%)	162 (16%)
Birth weight	g, mean (SE)	1,260 (24)	1262 (17)
	g, range	465 - 3935	358 - 3550
Prior hospitalizations	none, n (%)	53 (11%)	98 (10%)
	1 - 2, n (%)	384 (77%)	813 (81%)
	> 2, n (%)	63 (13%)	90 (9%)
	unknown, n (%)	0	1 (0.1%)
Prior RSV infections	Yes, n (%)	28 (6%)	38 (4%)
Prior LRI	Yes, n (%)	125 (25%)	231 (23%)
Entry LRI Score	≤ 2, n (%)	496 (99%)	982 (98%)
	> 2, n (%)	4 (0.8%)	19 (2%)
	unknown, n (%)	0	1 (0.1%)
Number in household**	n, mean (SE)	3.5 (0.1)	3.5 (0.1)
	n, range	1 - 13	1 - 13
Smokers in household	0, n (%)	343 (69%)	631 (63%)
	1, n (%)	106 (21%)	229 (23%)
	2, n (%)	41 (8%)	126 (13%)
	> 2, n (%)	10 (2%)	16 (2%)
Family history	of asthma, n (%)	176 (35%)	362 (36%)
	of hay fever, n (%)	148 (30%)	287 (29%)
	of eczema, n (%)	82 (16%)	165 (17%)
RSV neutralizing antibody	≥ 1:200, n (%)	28 (6%)	55 (6%)
	< 1:200, n (%)	417 (83%)	828 (83%)
	not done, n (%)	55 (11%)	119 (12%)
In day care	Yes, n (%)	34 (7%)	67 (7%)

**excluding subject

An LRI score of ≤ 2 indicates mild or even less than mild LRI

Table 20 presents baseline characteristics that were not prospectively identified for analysis in the protocol/analytical plan. These characteristics represent this reviewer's or the sponsor's exploratory analysis of the CRF/data sets.

Table 20. Baseline Characteristics Not Identified Prospectively for Analysis

Characteristic		Placebo n = 500	MEDI-493 n = 1002
BPD diagnosis	Yes, n (%)	266 (53%)	496 (50%)
With oxygen in past 6 months	Yes, n (%)	227 (45%)	409 (41%)
With oxygen ongoing	Yes, n (%)	65 (13%)	158 (16%)
With steroids in past 6 months	Yes, n (%)	158 (32%)	284 (28%)
With steroids ongoing	Yes, n (%)	43 (9%)	78 (8%)
Treated with RespiGam™	Yes, n (%)	5 (1%)	18 (2%)

Comment: The two groups appear to be well balanced with respect to baseline characteristics. The distribution of these characteristics was not remarkably different when analyzed in country (USA, UK, Canada) subsets. Overall, the mean age of subjects was 6 months and the mean weight 5 kg. Most of the subjects were premature and had been hospitalized at least once since birth. Approximately 80% of the subjects had a gestational age ≤ 32 weeks.

9.0.0 Compliance with Dose Regimen:

Table 21 describes the compliance with the injection regimen.

Table 21. Extent of Drug Exposure

Number of injections	Placebo n = 500	MEDI-493 n = 1002
0	3 (0.6%)	1 (0.1%)
1	10 (2.0%)	21 (2.1%)
2	3 (0.6%)	7 (0.7%)
3	5 (1.0%)	18 (1.8%)
4	10 (2.0%)	30 (3.0%)
5	469 (93.8%)	925 (92.3%)

Comment: Compliance with the study agent appears appropriate. These data suggest the product is tolerated well.

10.0.0 Results:

10.1.0 Primary Endpoint:

The primary endpoint of the trial was a comparison of the rates of RSV hospitalization. In this rate analysis all subjects randomized are included in the denominator and all subjects who are admitted to the hospital for RSV disease are included in the numerator. A patient lost to follow-up or who died without sustaining an RSV hospitalization was not to be included in the numerator. Additionally, each patient is counted only once in the analysis--only the first of multiple hospitalizations for RSV disease was counted in this calculation. Table 22 shows the primary endpoint result.

Table 22. RSV Hospitalization (Primary Endpoint)

Outcome	Placebo n = 500	MEDI-493 n = 1002	P*
RSV hospitalization, n (%)	53 (10.6%)	48 (4.8%)	< 0.00001
No RSV hospitalization, n (%)	447 (89.4%)	944 (95.2%)	
RSV hospitalization rate difference, MED-493 - Placebo	5.8%, 95% CI 2.8%, 8.8%		

*Fisher's Exact test

The statistical analysis SOP supplement to the protocol identified (prospectively) three exploratory analyses of the primary endpoint:

-sensitivity analysis where subjects who die, lost to follow-up or who have a respiratory hospitalization but no RSV antigen are counted as RSV hospitalizations
-a logistic regression analysis of the rates where covariates include all prospectively defined baseline characteristics that differ between treatment groups ($p \leq 0.05$) and that include sex, age, BPD and weight at study entry; two models were to be created, the first was to include the covariates and test for covariate by treatment interactions, the second model was to contain only main effects. An overall test of interaction was to be analyzed by using the difference between the log likelihood for these two models.
-the rates of RSV hospitalization will be estimated using Kaplan-Meier curves and calculated as the difference in time from date of randomization to either date of study completion, date of last contact, or date of RSV hospitalization. The two curves were to be compared using a logrank statistic.

Comment: These data show an absolute reduction in the risk for RSV hospitalization of 5.8%. This implies that the number needed to treat to avoid one hospitalization is 17. The relative risk reduction for RSV hospitalization is 55%. Consequently, administering MEDI-493 more than halves the risk for RSV hospitalization.

These prospectively planned exploratory analyses are shown below.

10.1.1 Primary Endpoint Sensitivity Analyses:

The number of subjects affecting the numerator in the rate calculation is shown in Table 23.

Table 23. Number of Subjects with No Primary Endpoint Data Available

Outcome	Placebo	MEDI-493
Respiratory hospitalization but no RSV antigen	3	6
Died without reaching primary endpoint	5	2
Lost to follow-up	0	5
Withdrew consent	0	4
Total	8	17

The sponsor chose to perform the sensitivity analysis using an adjustment for the number of subjects with missing primary endpoint data. In this adjustment the rate of RSV hospitalization in the alternative group was used to estimate the number of subjects to be included in the sensitivity analysis. The sponsor performed this analysis noting that there were 11 subjects in the MEDI-493 group who did not complete the study. Consequently, the sponsor added one subject to the numerator of the MEDI-493 rate (0.106 X 11 = 1) and no subjects to the numerator of the placebo rate. This result is shown in Table 24.

Table 24. Sponsor's Sensitivity Analysis of Primary Endpoint

Outcome	Placebo n = 500	MEDI-493 n = 1002	P*
Adjusted for missing data	53 (10.6%)	49 (4.9%)	0.0001

*Fisher's Exact test

Table 25 shows a sensitivity analysis performed in which all the missing data are incorporated. This analysis was described in the analytical plan SOP, but was not included in the BLA submission. Table 25 is an FDA analysis.

Table 25. Sensitivity Analysis of Primary Endpoint Using All Missing Data

Outcome	Placebo n = 500	MEDI-493 n = 1002	P*
Known outcomes + all missing subjects assumed to have RSV hospitalizations	61 (12.2%)	65 (6.5%)	0.0002
Known outcomes + only the missing MEDI-493 subjects assumed to have RSV hospitalizations	53 (10.6%)	65 (6.5%)	0.006

Comment: These analyses suggest that the missing data have minimal impact upon the primary endpoint results.

10.1.2 Logistic Regression Analysis of Baseline Characteristics/Primary Endpoint Result:

The sponsor noted that none of the prospectively identified baseline characteristics differed between the two groups statistically. Consequently, their logistic regression analysis included only the four major predictors of RSV hospitalization identified in the analytical SOP (sex, entry age, diagnosis and entry weight). The sponsor notes in the study report that treatment with MEDI-493 remained significant (p , 0.001) with these other variables included in a regression model. Table 26 is a duplicate of the sponsor's presentation of logistic regression results.

Table 26. Logistic Regression of Incidence of RSV Hospitalization

Variable	Parameter estimate	p-value	Odds Ratio	95% CI of Odds Ratio
Treatment (MEDI-493)	-0.856	<0.001	0.425	(0.28, 0.64)
Gender (Males)	0.175	0.422		
Entry Age (Months)	-0.014	0.773		
Diagnosis (BPD)	1.174	<0.001		
Entry Weight (Kg)	-0.105	0.257		

Comment: We have verified the Table 26 result using the SAS data sets. We also analyzed the baseline characteristics to determine which were associated with a higher risk of RSV hospitalization. Among selected covariates (diagnosis, oxygen use, steroid use), only diagnosis of BPD was associated with a higher risk for RSV hospitalization. In general, MEDI-493 appears effective in both patients with prematurity but no BPD and those with BPD. However, the greatest effect is within the subset of premature patients.

10.1.3 Kaplan-Meier Analysis of Primary Endpoint Result:

The sponsor notes in the study report that the Kaplan-Meier estimate of RSV hospitalization at 150 days was identical to the result from the primary comparison of hospitalization rates (10.6% in the placebo group and 4.8% in the MEDI-493 group, p<0.001).

10.1.4 RSV Hospitalization by Month:

This was an exploratory analysis performed by the sponsor. Table 27 is a duplicate of the sponsor's summary.

Table 27. Incidence of RSV Hospitalization by Month

Subjects with RSV Hospitalization	Placebo n = 500	MEDI-493 n = 1002
Total	53 (10.6%)	48 (4.8%)
November 15-30	0 (0%)	4 (0.4%)
December	10 (2.0%)	9 (0.9%)
January	18 (3.6%)	11 (1.1%)
February	18 (3.6%)	16 (1.6%)
March	3 (0.6%)	6 (0.6%)
April	3 (0.6%)	2 (0.2%)
May 1-15	1 (0.2%)	0 (0%)

10.1.6 RSV Hospitalization by country/site:

This was an exploratory analysis performed by the sponsor. Table 28 is a summary of the sponsor's analysis.

Table 28. RSV Hospitalization by Country

Country, n # RSV Hospitalizations	**Placebo**	**MEDI-493**
USA	n = 426	n = 851
RSV Hospitalizations	44 (10.3%)	39 (4.6%)
UK	n = 40	n = 83
RSV Hospitalizations	4 (10.0%)	3 (3.6%)
Canada	n = 34	n = 68
RSV Hospitalizations	5 (14.7%)	6 (8.8%)

The analytical plan did not call for analysis of the primary endpoints by sites. The FDA performed the following analysis. There were 139 study sites, the largest of which enrolled 25 patients. In Table 29, the incidence of RSV hospitalization in every study site enrolling more than 17 patients is tabulated in order by size. These 15 sites accounted for approximately 20% of the total study participants.

Table 29. Primary Endpoint in Sites Enrolling > 17 Patients

Site	MEDI-493 RSV Hosp/ total	Placebo RSV Hosp/ total	All patients RSV hosp/ total
053	0/16	0/9	0/25
090	0/15	0/8	0/23
239	0/14	0/7	0/21
227	0/14	1/7	1/21
073	1/14	2/7	3/21
274	0/13	3/7	3/20
187	0/14	0/6	0/20
136	1/13	0/6	1/19
273	1/13	0/6	1/19
179	1/12	1/7	2/19
207	0/12	0/6	0/18
109	0/12	0/6	0/18
072	0/12	1/6	1/18
050	2/12	1/6	3/18
038	0/12	0/6	0/18
Total (%)	6/198 (3.0%)	10/101 (9.9%)	16/299 (5.4%)

Table 30 shows the results of the primary endpoint in the sites with the highest number of events. This analysis includes:

-any site with at least 4 cases of RSV hospitalization , or

-any site with at least 3 cases of RSV hospitalization and an overall incidence of at least 20%, or
-any site with at least 2 cases of RSV hospitalization and an overall incidence of at least 20% in either one of the trial arms

Table 30. Primary Endpoint in Sites with the Highest Numbers of Events

Site	MEDI-493 RSV hosp/ total	Placebo RSV hosp/ total	All patients RSV hosp/ total
073	1/14	2/7	3/21 (14%)
274	0/13	3/7	3/20 (15%)
142	2/10	3/5	5/15 (33%)
231	4/10	1/5	5/15 (33%)
110	2/10	0/5	2/15 (13%)
037	2/8	1/4	3/12 (25%)
205	1/8	2/4	3/12 (25%)
214	2/8	0/4	2/12 (17%)
188	1/7	3/4	4/11 (36%)
224	1/5	2/2	3/7 (43%)
152	2/4	0/2	2/6 (33%)
Total (%)	18/97 (19%)	17/49 (35%)	35/146 (24%)

Comment: These analyses show consistent treatment effects across countries and sites.

10.1.7 Primary Endpoint in Subsets:

The SOP for the statistical plan identified certain subsets to be analyzed in an exploration of the primary endpoint. These subsets were to examine the following: entry age, gestational age, race, sex, entry weight, BPD, and country. Table 31 is a duplicate of the sponsor's subset analyses. The specific categories were prespecified in the SOP.

Table 31. Planned Primary Endpoint Subset Analyses

Subset	Characteristic	Placebo n = 500	MEDI-493 n = 1002	RR
Sex	Male	37/284 (13.0%)	25/570 (4.4%)	0.34
	Female	16/216 (7.4%)	23/432 (5.3%)	0.72
BPD	No	19/234 (8.1%)	9/506 (1.8%)	0.22
	Yes	34/266 (12.8%)	39/496 (7.9%)	0.62
Entry Age	≤ 6 months	35/342 (10.2%)	28/698 (4.0%)	0.39
	> 6 months	18/158 (11.4%)	20/304 (6.6%)	0.58
Gestational Age	≤ 32 weeks	47/417 (11.3%)	44/840 (5.2%)	0.46
	> 32 weeks	6/83 (7.2%)	4/162 (2.5%)	0.34
Entry Weight	≤ 5 Kg	30/285 (10.5%)	27/600 (4.5%)	0.43
	> 5 Kg	23/215 (10.7%)	21/402 (5.2%)	0.49
Race	Caucasian	31/287 (10.8%)	24/585 (4.1%)	0.38
	Black	14/128 (10.9%)	12/228 (5.3%)	0.56*
	Hispanic	5/54 (9.3%)	7/110 (6.4%)	
	Asian	3/12 (25%)	0/21 (0%)	
	Other	0/19 (0%)	5/58 (8.6%)	
Country	USA	44/426 (10.3%)	39/851 (4.6%)	0.44
	UK	4/40 (10%)	3/83 (3.6%)	0.49**
	Canada	5/34 (14.7%)	6/68 (8.8%)	

*RR for Hispanic, Asian and Other, combined
**RR for UK and Canada, combined
RR indicates relative risk (MEDI-493/placebo)

Comment: The SOP noted that no p values would be calculated for these subset analyses. In the above

data all subsets have p-values < 0.05 except the following:

Subset	p-value
Female Sex	0.298
Entry Age > 6 months	0.107
Race: Black	0.057
Country: UK	0.213
Country: Canada	0.499

These values are probably indicative of low sample sizes. The trial was not designed to test outcomes in specific subsets. The finding of greater efficacy in males is consistent with the data which suggest RSV is more severe in males.

Table 32 presents a subset analysis of the primary endpoint among groups that were not described in the protocol or statistical SOP. This table is exploratory and generated by the FDA.

Table 32. Additional Primary Endpoint Subset Analyses

Subset	Characteristic	Placebo n = 500		MEDI-493 n = 1002		RR
Steroids within past 6 months	Yes	21/158	(13.3%)	24/284	(8.5%)	0.64
	No	32/342	(9.4%)	24/718	(3.3%)	0.35
Ongoing steroid therapy	Yes	2/43	(4.6%)	5/78	(6.4%)	1.39
	No	51/457	(11/2%)	43/924	(4.6%)	0.41
Prior LRTI hospitalization	Yes	11/71	(15.5%)	10/104	(9.6%)	0.62
	No	42/429	(9.8%)	38/898	(4.2%)	0.43
With oxygen in past 6 months	Yes	28/227	(12.3%)	35/409	(8.6%)	0.70
	No	25/273	(9.2%)	13/593	(2.2%)	0.24
With oxygen ongoing	Yes	7/65	(10.8%)	16/158	(10.1%)	0.94
	no	46/435	(10.6%)	32/844	(3.8%)	0.36
Multiple birth	Yes	10/137	(7.3%)	14/318	(4.4%)	0.60
	No	43/363	(11.8%)	34/684	(5.0%)	0.42

RR = relative risk for RSV hospitalization, MEDI-493 divided by placebo; a RR > 1 indicates an increased risk for RSV hospitalization for the MEDI-493 group

These data show that MEDI-493 works less well in the sickest infants--in those with oxygen ongoing, with ongoing steroid use or oxygen use within the past six months.

It is of some concern that MEDI-493 treatment failures may be related to RSV isolates that are not neutralized by MEDI-493. The sponsor notes that there were 15 positive RSV cultures among the 48 MEDI-493 patients who had RSV hospitalizations. Only 10 of these samples were frozen and submitted to the central laboratory. Of these 10 samples only five could be propagated . Three of these five isolates were neutralized by MEDI-493, two isolates are currently being tested.

Table 33 presents analyses on compliance and the primary endpoint (these are exploratory analyses and were not prespecified analyses). Note that approximately 94% of placebo patients who were either not hospitalized for RSV or were hospitalized for RSV had received all 5 injections. In the MEDI-493 arm, approximately 93% of the patients who were not hospitalized with RSV had received all 5 injections , while only 77% of the patients who were hospitalized with RSV received all 5 injections.

Table 33. Compliance and RSV Hospitalization

Received:	MEDI-493		Placebo		Total n = 1502
	RSV Hosp n = 48	No RSV Hosp n = 954	RSV Hosp n = 53	No RSV Hosp n = 447	
All 5 injections	37 (77.1%)	888 (93.1%)	50 (94.3%)	419 (93.7%)	1394 (92.8%)
< 5 injections	9 (18.8%)	66 (6.9%)	3 (5.7%)	28 (6.3%)	106 (7.1%)
Total	48 (100%)	954 (100%)	53 (100%)	447 (100%)	1502 (100%)

Comment: In general, subset analyses show consistent effects and it is not possible to clearly identify an especially notable subset of patients who do not receive benefit. Many of the subset sizes are too small to reach notable impressions. The compliance subset finding (given that there are not remarkable AE findings) is consistent with a treatment effect.

According to the trial protocol, each patient was to be counted only once in the calculation of RSV hospitalizations. There were four patients who had more than one RSV hospitalization. These data are shown in Table 34. No patient had more than two RSV hospitalizations.

Table 34. Patients with More than One RSV Hospitalization

Patient #	Agent	RSV Adm Date	RSV Disch Date
[redacted]	Placebo	27FEB97 15APR97	01MAR97 17APR97
	MEDI-493	20NOV96 04DEC96	04DEC96 12DEC96
	MEDI-493	10JAN97 16Jan97	14JAN97 22JAN97
	MEDI-493	04MAR97 14MAR97	08MAR97 14MAR97

10.1.8 Primary endpoint and other hospitalizations:

Table 35 summarizes all hospitalizations in the trial.

Table 35. All Hospitalizations

Agent	Number of Hospitalizations for:			Total Hospitalizations
	RSV	Non-RSV	Non-resp	
Placebo	54	103	72	229
MEDI-493	52	182	143	377
Total	106	285	215	606

Comment: These data show that the reduction in the number of RSV hospitalizations among patients receiving MEDI-493 did not come at the expense of a higher number of other types of hospitalizations.

10.2.0 Secondary endpoints:

The protocol and statistical plan SOP called for examination of secondary endpoints in the following three areas:

-descriptors of the RSV hospital course
-descriptors of non-RSV hospitalizations
-incidence of otitis media.

The following secondary endpoints are presented in the order they were described in the statistical plan SOP. The secondary endpoints were not ordered according to significance/importance or anticipated result.

10.2.1 RSV hospital course secondary endpoints:

The following secondary endpoints were to be analyzed.

1. Total days in hospital due to RSV
2. Total RSV hospital days with increased supplemental oxygen
3. Total RSV days with LRI score ≥ 3
4. Incidence and total days of RSV ICU stay
5. Incidence and total days of RSV related mechanical ventilation

Table 36 presents the sponsor's summary of these outcomes.

Table 36. RSV Hospital Course Secondary Endpoints

RSV Hospital Outcome	Measure	Placebo n = 500	MEDI-493 n = 1002	p-value*
Days of hospitalization	Total days	313.1	364.6	-
	Total days/100 subjects	62.6	36.4	< 0.001
Days of increased oxygen	Total days	253.0	304.0	-
	Total days/100 subjects	50.6	30.3	< 0.001
Days with LRI score ≥ 3	Total days	237.0	297.0	-
	Total days/100 subjects	47.4	29.6	< 0.01
ICU admission	Yes	15 (3.0%)	13 (1.3%)	0.026
	No	485	989	-
Days ICU stay	Total days	63.5	133.6	-
	Total days/100 subjects	12.7	13.3	0.023**
Mechanical ventilation	Yes	1 (0.2%)	7 (0.7%)	0.282
	No	499	995	-
Days of mechanical ventilation	Total days	8.3	83.7	-
	Total days/100 subjects	1.7	8.4	0.211**

*incidence of ICU and mechanical ventilation were compared using Fisher's Exact test, all other outcomes were compared using Wilcoxon rank sum test

***The sponsor's draft of the PI includes a table of "Summary of IMpact-RSV Trial Results" which does not include these two outcomes. All other secondary endpoints relating to RSV hospitalization are included in the sponsor's draft table.*

Comment: It is notable that the incidence of mechanical ventilation was higher in the MEDI-493 group. The difference was not statistically greater and it is unclear as to the significance of the observation. The PI for the product should include the mechanical ventilation results and all other prospectively identified RSV hospitalization secondary endpoints--not just the successful ones.

These data may also be compared only in the subset of subjects hospitalized with RSV. Table 37 presents these data for only the subset of subjects with RSV hospitalization.

Table 37. RSV Hospital Course in the Subset of RSV Hospitalized Subjects

RSV Hospital Outcome	Measure	Placebo n = 53	MEDI-493 n = 48
Days of hospitalization	Total days/subject	5.9	7.6
Days of increased oxygen	Total days/subject	4.8	6.3
Days with LRI score ≥ 3	Total days/subject	4.5	6.2
ICU admission	Yes	15 (28%)	13 (27%)
	No	38	35
Days ICU stay	Total days/subject	1.2	2.8
Mechanical ventilation	Yes	1 (2%)	7 (14.6%)
	No	52	41
Days of mechanical ventilation	Total days/subject	0.2	1.7

These findings are not unexpected. MEDI-493 appears to decrease the incidence of RSV hospitalization. To say that MEDI-493 decreases the severity of RSV illness will require an interpretation of the data similar to that utilized for RespiGam™--ie., if severity comparisons are made according to the following formula:

$$\text{severity of illness} = \frac{\text{number of RSV hospitalizations}}{\text{number of RSV illnesses}}$$

we have data only for the number of RSV hospitalizations and not for the number of RSV illnesses. To say that MEDI-493 decreases the severity of RSV illness assumes that the number of RSV illnesses between the two trial arms is the same. This assumption was made for RespiGam™.

The hospitalization findings in the MEDI-493 group are driven by the findings from four patients who had exceptionally long and complicated hospital courses. Figure 4 shows the distribution of RSV hospitalization days by treatment arm.

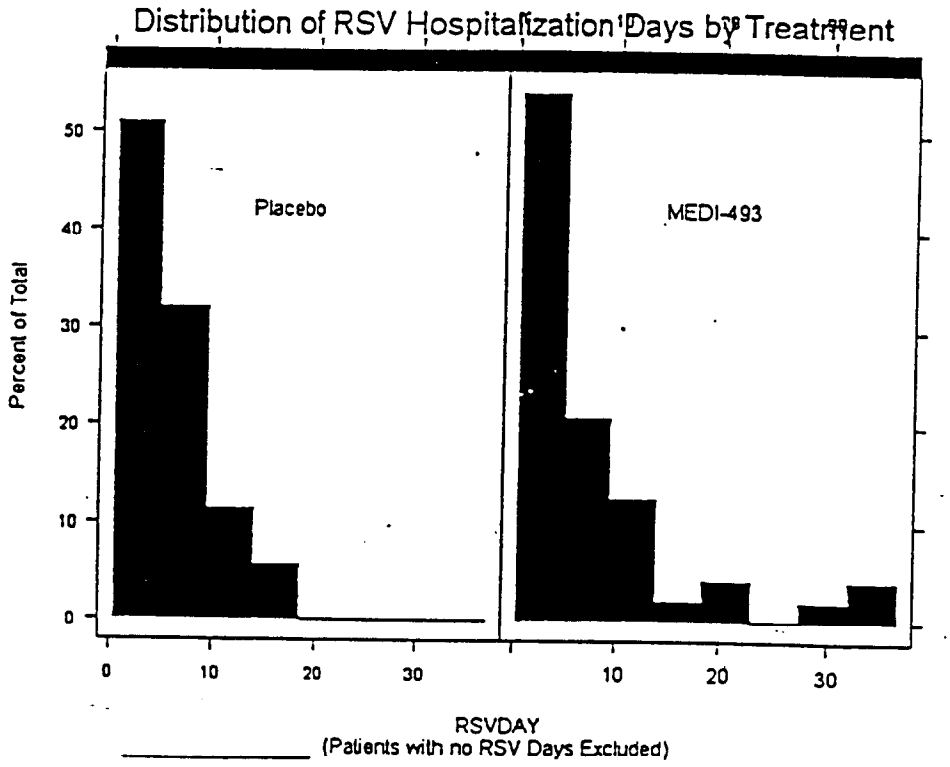


Figure 4. Distribution of RSV Hospitalization Duration

A total of seven patients were hospitalized for at least 15 days. Six of these patients were in the MEDI-493 arm and two were in the placebo arm. Table 38 shows the hospitalization information for these seven patients.

Table 38. Hospitalization Information for Patients who were Hospitalized ≥ 15 Days

Patient #	Agent	# RSV Hosp Days	# ICU Days	# Days Mech Vent	# Days Supp Oxy	# Days Hosp Total*
	placebo	18	18	0	19	18
	placebo	15	7	0	13	37
	MEDI-493	35	30	19	37	64
	MEDI-493	36	28	17	26	38
	MEDI-493	17	15	10	15	24
	MEDI-493	31	21	19	27	34
	MEDI-493	19	3	0	17	19
	MEDI-493	19	0	0	17	43

*hospitalization was prolonged for some patients after recovery from RSV (surgery, wait gain, etc)

Rather than looking at certain hospitalization outcomes separately , we considered them together as parts of a spectrum of events which occurred in the study. The events were ordered by severity of outcome, the worst outcome being death, followed by mechanical ventilation, ICU admission, supplemental oxygen required, RSV hospitalization or none of these. Each patient was classified according to their worst outcome category. Table 39 shows these results when all study deaths are included in this analysis. Of the nine patients who died in the study , only two patients, both in the MEDI-493 arm, died during RSV hospitalization. None of the other seven patients were hospitalized for RSV infection.

Table 39. Ordered Outcomes, Including All Deaths

Agent	Dead	Mech Vent	Admitted to ICU	Required supple oxy	RSV Hosp	No RSV Hos	Total
MEDI-493	4 (0.4%)	5 (0.5%)	6 (0.6%)	20 (2.0%)	15 (1.5%)	952 (95%)	1002 (100%)
Placebo	5 (1.0%)	1 (0.2%)	14 (2.8%)	25 (5.0%)	13 (2.6%)	442 (88%)	500 (100%)
Total	9 (0.6%)	6 (0.4%)	20 (1.3%)	45 (3.0%)	28 (1.9%)	1394 (93%)	1502

Using StatXact, an exact Komolgorov-Smirnov test was used to test equality of the two distributions. The evidence that the group treated with MEDI-493 had better outcomes (stochastically larger) was very strong, with a p-value < 0.0001.

However, if only the RSV hospitalization outcomes are considered in such an analysis (with only two deaths in the table--both in the MEDI-493 arm), the above conclusion cannot be reached (Table 40).

Table 40. Ordered Outcomes, Including Only RSV Hospitalization Outcomes

Agent	Dead	Mech Vent	Admitted to ICU	Required supple oxy	RSV Hosp	Total
MEDI-493	2	5	6	20	15	48
Placebo	0	1	14	25	13	53
Total	2	6	20	45	28	101

10.2.2 Non-RSV hospitalization secondary endpoints:

The following endpoints were identified in the statistical plan SOP for analysis:

6. Incidence and total days of non-RSV respiratory hospitalization, any respiratory hospitalization, and hospitalization for any cause

In this analysis a subject with more than one hospitalization within a certain category was to be counted only once. Table 41 is the sponsor's summary of the hospitalization data.

Table 41. Hospitalization

Outcome	Measure	Placebo n = 500	MEDI-493 n = 1002	P*
Children with Hospitalization for any cause	Number	153 (30.6%)	244 (24.4%)	0.011
	Total days	1210.9	1915.6	
	Total days/100 subjects	242	191	0.005
Children with Respiratory hospitalization	Number	109 (21.8%)	161 (16.1%)	0.008
	Total days	901.6	1246.7	
	Total days/100 subjects	180.3	124.4	0.004
Children with Non-RSV respiratory hospitalization	Number	72 (14.4%)	130 (13.0%)	0.470
	Total days	588.5	882.0	
	Total days/100 subjects	117.7	88.0	0.369

*incidence of hospitalization was compared using Fisher's Exact test, all other outcomes are compared using Wilcoxon rank sum test

Comment: Table 42 is a duplicate of the sponsor's analysis. This table has been verified . This analysis is complicated by some children having more than one type of hospitalization .

10.2.3 Otitis Media:

The final (seventh) secondary endpoint was a comparison of the incidence of otitis media. These results are shown in Table 42.

Table 42. Otitis Media

Outcome	Placebo n = 500	MEDI-493 n = 1002	P*
Number of episodes	364	694	
Number of subjects with at least one episode	200 (40.0%)	420 (41.9%)	0.505
Number of episodes/ subjects	0.73	0.69	

*Fishers' Exact test

10.3.0 Pharmacological Results:

The dose of MEDI-493 was chosen based upon preclinical studies which showed that serum levels of 25 to 40 mcg/mL resulted in less RSV in the lungs of animals challenged with RSV. Subjects were to have MEDI-493 serum levels determined at baseline and prior to the fifth injection. Subjects were assigned to have additional blood levels obtained prior to other injections (random subjects). Only subjects who received injections were to be included in these analyses.

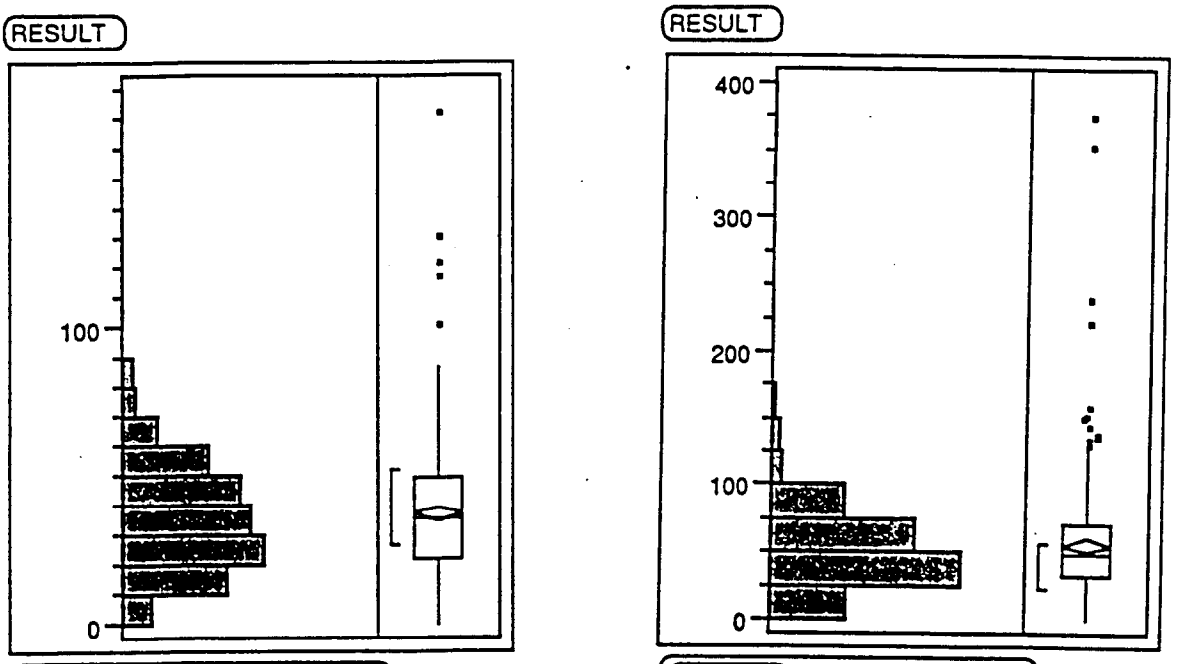
Table 43 presents the results of serum MEDI-493 levels and Figure 5 shows the distribution of these data.

Table 43. MEDI-493 Serum Concentrations (mcg/mL)

Time Point	Serum Concentration	
Baseline (pre-injection # 1) n = 922	mean (SE)	0.0 (0.0)
	median	0.0
	range	0.0 - 0.0
Pre-injection # 2 n = 328	mean (SE)	37.4 (1.2)
	median	35.6
	range	0.0 - 173
Pre-injection # 3 n = 300	mean (SE)	56.5 (2.4)
	median	49.8
	range	0.0 - 378
Pre-injection # 4 n = 297	mean (SE)	67.5 (2.9)
	median	62.8
	range	0.0 - 590
Pre-injection # 5 n = 892	mean (SE)	71.9 (1.7)
	median	63.2
	range	0.0 - 839.5

Comment: Compliance in obtaining blood samples was very good and the results demonstrate that the target levels were achieved.

892 patients had blood levels of MEDI-493 obtained at the fifth injection. A small number of patients (63, 7%) had blood levels >144 mcg/mL (2 times the fifth injection mean). The distribution of these blood levels is shown in Figure 5.



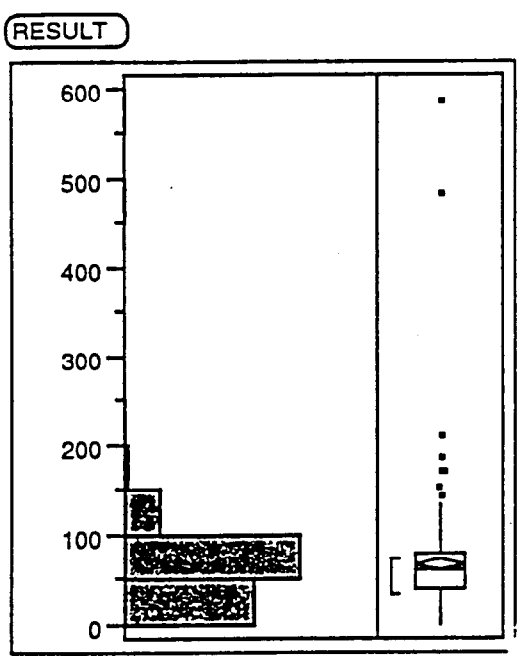
Quantiles		
maximum	100.0%	172.76
	99.5%	146.33
	97.5%	83.63
	90.0%	61.62
quartile	75.0%	49.31
median	50.0%	35.60
quartile	25.0%	22.13
	10.0%	13.52
	2.5%	7.26
	0.5%	0.00
minimum	0.0%	0.00

Moments	
Mean	37.3922
Std Dev	21.3629
Std Error Mean	1.1796
Upper 95% Mean	39.7128
Lower 95% Mean	35.0717
N	328.0000
Sum Weights	328.0000

Quantiles		
maximum	100.0%	377.52
	99.5%	365.47
	97.5%	149.32
	90.0%	90.58
quartile	75.0%	72.10
median	50.0%	49.84
quartile	25.0%	32.94
	10.0%	21.17
	2.5%	10.93
	0.5%	0.00
minimum	0.0%	0.00

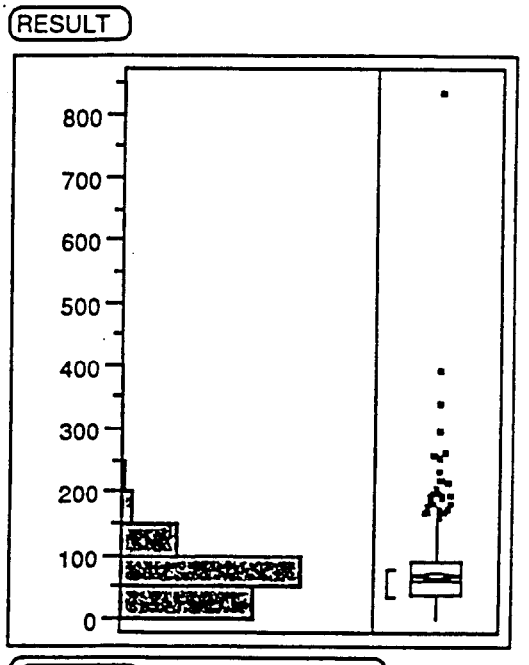
Moments	
Mean	56.4793
Std Dev	40.9866
Std Error Mean	2.3664
Upper 95% Mean	61.1362
Lower 95% Mean	51.8224
N	300.0000
Sum Weights	300.0000

Figure 5. MEDI-493 Blood Levels at the Second (left) and Third (right) Injections



Quantiles		
maximum	100.0%	590.03
	99.5%	539.57
	97.5%	150.62
	90.0%	112.43
quartile	75.0%	81.69
median	50.0%	62.77
quartile	25.0%	41.06
	10.0%	26.47
	2.5%	14.85
	0.5%	0.00
minimum	0.0%	0.00

Moments	
Mean	67.5185
Std Dev	50.7320
Std Error Mean	2.9438
Upper 95% Mean	73.3119
Lower 95% Mean	61.7250
N	297.0000
Sum Weights	297.0000



Quantiles		
maximum	100.0%	839.51
	99.5%	285.88
	97.5%	185.66
	90.0%	118.53
quartile	75.0%	91.26
median	50.0%	63.19
quartile	25.0%	42.25
	10.0%	26.54
	2.5%	14.56
	0.5%	0.00
minimum	0.0%	0.00

Moments	
Mean	71.9000
Std Dev	50.2404
Std Error Mean	1.6822
Upper 95% Mean	75.2015
Lower 95% Mean	68.5984
N	892.0000
Sum Weights	892.0000

Figure 5. (continued) MEDI-493 Blood Levels at the Fourth (left) and Fifth (right) Injections

Table 44 presents the MEDI-493 serum concentrations among the MEDI-493 group patients at the time of RSV Hospitalization.

Table 44. MEDI-493 Serum Concentration (mcg/mL) at time of RSV Hospitalization

Patients with RSV Hospitalization, n = 48	Serum Concentration	
Patients with serum levels, n =	mean (SE)	84.0
	range	0.0 - 218.0

Only subsets of patients had MEDI-493 blood levels determined at the second, third and fourth injection times. All patients were to have MEDI-493 blood levels obtained at the fifth injection.

Comment: The large range of values at the fifth injection point is due to four patients who had blood levels greater than 200 mcg/mL Overall, 21 patients had at least one blood level greater than 200 mcg/mL and all of these occurred at the time of the third, fourth or fifth injections. There was not a disproportionate number of adverse events in patients who had blood levels greater than 200 mcg/mL. There were 100 AE among the 21 patients and only one was rated as severe. Notably, the patient with the MEDI-493 blood level of approximately 840 mcg/mL experienced no adverse events.

Table 45 presents summarizes the AE when the patients are divided into quartiles according to the MEDI-493 blood level at the fifth injection.

Table 45. AE by MEDI-493 Blood Concentration

Outcome	Quartile 1*	Quartile 2*	Quartile 3*	Quartile 4*
n	223	223	223	223
Number with any AE (%)	217 (97.3%)	217 (97.3%)	216 (96.9%)	213 (95.5%)
Number with serious AE (%)	79 (35.4%)	68 (30.5%)	58 (26.0%)	54 (24.2%)
Number with severe AE (%)	42 (18.8%)	40 (17.9%)	35 (15.7%)	23 (10.3%)
Number with life threatening AE (%)	15 (6.7%)	9 (4.0%)	2 (0.9%)	7 (3.1%)

*The range for quartiles (mcg/mL) are: Q1 (0, <42.3); Q2 (42.3, <63.2), Q3 (63.2, < 91.3), Q4 (91.3, < 839.5)

Comment: These data suggest that MEDI-493 is well tolerated. It is notable that patients with more severe AE tended to have lower MEDI-493 blood levels, suggesting that sicker infants may clear the agent more rapidly than healthy infants.

10.4.0 Safety Results:

Safety analyses that were prospectively defined included descriptions of immunoreactivity to MEDI-493, adverse events and clinical chemistry. These are described below.

10.4.1 Immunoreactivity to MEDI-493

The results of serum immunoreactivity to MEDI-493 are shown in Table 46. There was a total of 25 patients with antibody titers > 1:40 (14 patients in the placebo group and 12 patients in the MEDI-493 group). One patient in each group had reactive samples at two different time points.

Table 46. Serum Antibodies to MEDI-493

Time	n	Placebo	MEDI-493
Pre-injection # 1	number assayed (% total)	458 (91.6%)	917 (91.5%)
	Titer > 1:40	0	0
Pre-injection # 2	number assayed (% total)	134 (26.8%)	318 (31.7%)
	Titer > 1:40 (% assayed)	1 (0.7%)	2 (0.6%)
Pre-injection #3	number assayed (% total)	155 (31.0%)	281 (28.0%)
	Titer > 1:40 (% assayed)	6 (3.9%)	4 (1.4%)
Pre-injection #4	number assayed (% total)	151 (30.2%)	275 (27.4%)
	Titer > 1:40 (% assayed)	3 (2.0%)	1 (0.4%)
Pre-injection #5	number assayed (% total)	436 (87.2%)	862 (86.0%)
	Titer > 1:40 (% assayed)	5 (1.1%)	6 (0.7%)

Comment: There was no remarkable development of antibodies to MEDI-493. Even though the last antibody time point was prior to the fifth injection, these data are adequate to rule out significant immunogenicity of the product.

10.4.2 Adverse events:

The AE reporting process was prospectively defined in the protocol. An AE was any adverse change from the baseline medical condition. Each AE was to be graded for severity (mild, moderate, severe, life threatening) and was to be assessed by the blinded investigator as to potential relationship to the study agent. The protocol included a toxicity table as a guideline (adapted from the AIDS Clinical Trial Group Pediatric Toxicity Tables). Table 47 shows the summary of AE and Table 48 shows the common AE in which the incidence was greater in the MEDI-493 group than in the placebo group (using COSTART preferred terms). Table 49 shows the less common AE in which the incidence was greater in the MEDI-493 group than in the placebo group.

Table 47. Adverse Event Summary

Outcome	Placebo	MEDI-493	P*
Total number of children reporting one or more AE (%)	482 (96.4%)	961 (95.9%)	0.778
Total number of AE	2737	5417	-

*Fisher's Exact test

Table 48. Common Adverse Events with an Incidence higher in MEDI-493 Group

Event	Placebo n = 500	MEDI-493 n = 1002
URI	245 (49.0%)	527 (52.6%)
Otitis media	200 (40.0%)	420 (41.9%)
Rhinitis	117 (23.4%)	288 (28.7%)
Fever	134 (26.8%)	272 (27.1%)
Rash	112 (22.4%)	257 (25.6%)*
Cough	90 (18.0%)	186 (18.6%)
Wheeze	67 (13.4%)	138 (13.8%)
Pain	34 (6.8%)	85 (8.5%)
Hernia	25 (5.0%)	63 (6.3%)
SGOT increased	19 (3.8%)	49 (4.9%)*
SGPT increased	14 (2.8%)	29 (2.9%)
Injection site reaction (other)	11 (2.2%)	28 (2.8%)
Pharyngitis	7 (1.4%)	26 (2.6%)*
Study drug injection site reaction	9 (1.8%)	27 (2.7%)
Failure to thrive	5 (1.0%)	15 (1.5%)
Liver function test abnormal	4 (0.8%)	13 (1.3%)*
Anemia	6 (1.2%)	13 (1.3%)
Dyspnea	8 (1.6%)	12 (1.2%)

Table 49. Uncommon Adverse Events with an Incidence Higher in MEDI-493 Group

Event	Placebo n = 500	MEDI-493 n = 1002
Ecchymosis	4 (0.8%)	9 (0.9%)
Dehydration	3 (0.6%)	7 (0.7%)
Intestinal obstruction	1 (0.2%)	4 (0.4%)
Allergic reaction	1 (0.2%)	4 (0.4%)
Edema	1 (0.2%)	4 (0.4%)
Hydrocephalus	2 (0.4%)	5 (0.5%)
Parasitic infection	1 (0.2%)	4 (0.4%)
Neoplasm	0	1 (0.1%)
Overdose	0	2 (0.2%)
Skin ulcer	0	2 (0.2%)
Corneal lesion	0	1 (0.1%)
Eye hemorrhage	0	1 (0.1%)
Refraction disorder	0	1 (0.1%)
Strabismus	1 (0.2%)	3 (0.3%)
Abnormal vision	0	1 (0.1%)
Bladder calculus	0	1 (0.1%)
Breast enlargement	0	1 (0.1%)
Cystitis	0	1 (0.1%)
Genital edema	0	1 (0.1%)
Hematuria	0	3 (0.3%)
Labial adhesion	1 (0.2%)	3 (0.3%)
Female lactation	0	1 (0.1%)
Clubfoot	0	1 (0.1%)
Testes disorder	0	2 (0.2%)
Congenital anomaly	2 (0.4%)	5 (0.5%)
Asthenia	0	1 (0.1%)
Acne	0	1 (0.1%)
Hair disorder	0	1 (0.1%)
Herpes simplex	1 (0.2%)	3 (0.3%)
Mottled skin	0	2 (0.2%)
Skin benign neoplasm	0	2 (0.2%)
Peritonitis	0	1 (0.1%)
Rhonchi	0	2 (0.2%)
Stridor	0	2 (0.2%)
Rales	0	1 (0.1%)
Hyperventilation	2 (0.4%)	6 (0.6%)
Hypoventilation	0	1 (0.1%)
Hypoxia	1 (0.2%)	3 (0.3%)
Cardiomegaly	0	1 (0.1%)
Heart failure	0	1 (0.1%)

Abnormal heart sounds	3 (0.6%)	9 (0.9%)
Peripheral vascular disorder	0	1 (0.1%)
Abdominal enlargement	0	2 (0.2%)
Cholecystitis	0	1 (0.1%)
Cleft lip	0	1 (0.1%)
Dysphagia	1 (0.2%)	6 (0.6%)
Enteritis	0	2 (0.2%)
Gamma glutamyl transpeptidase increased	0	1 (0.1%)
Hepatitis	0	1 (0.1%)
Epistaxis	1 (0.2%)	3 (0.3%)
Melena	0	3 (0.3%)
Rectal disorder	0	1 (0.1%)
Hepatosplenomegaly	0	1 (0.1%)
Thrombocythemia	0	1 (0.1%)
Thrombocytopenia	0	2 (0.2%)
Bilirubinemia	0	1(0.1%)
BUN increased	4 (0.8%)	9 (0.9%)
CPK increased	0	1 (0.1%)
Creatinine increased	0	1 (0.1%)
Electrolyte depletion	0	1 (0.1%)
Hypercalcemia	0	1 (0.1%)
Hypervolemia	0	2 (0.2%)
Hypocalcemia	0	1 (0.1%)
Hypochloremia	0	1 (0.1%)
Weight loss	0	1(0.1%)
Hypertonia	0	10 (1.0%)*
Hypotonia	0	1(0.1%)
Ileus	0	1 (0.1%)
Insomnia	1 (0.1%)	3 (0.3%)
Mental retardation	0	3 (0.3%)
Myoclonus	0	2(0.2%)
Increased salivation	0	2 (0.2%)
Torticollis	0	3 (0.3%)
Intestinal stenosis	0	1 (0.1%)
Pyloric stenosis	0	1 (0.1%)
Hyperthyroidism	0	1 (0.1%)

Comment: Neither the types of AE or the incidence of AE is unexpected for this patient population. Only the slightly higher incidence of liver enzyme abnormalities seems notable when the MEDI-493 group is compared to the placebo group, but this elevation of SGOT is not statistically higher in the MEDI-493 group ($p = 0.340$) and the proportion of patients with elevated SGPT is similar.

In these tables, "injection site, other" refers to non-study agent injections (such as routine vaccinations). There was no evidence that the number of study agent injection site reactions was related to the number of injections. There were 21 injection site reactions after the first injection, 13 after the second injection, 12 after the third injection, 12 after the fourth injection and 2 after the fifth injection. Overall, no safety signals are evident from a review of AE data.

10.4.3 Adverse Events by Severity Assessment and Causal Relationship to Study Agent:

The protocol required that AE be assessed as to their severity by the site investigator. The severity assessment was based upon the grade assigned according to the protocol-defined toxicity table. Grades three and four in this toxicity table were defined as severe and life threatening, respectively. Grades one and two in the toxicity table corresponded with mild and moderate effects, respectively. The site investigator was also to assign a designation as to the causal relationship between each AE and the study agent. The categories of causal relationship were: none, remote, possible, probable and definite. The protocol provided guidelines for making these assignments. Table 50 shows the incidence of severe and life-threatening AE in the trial (only where the incidence in either the placebo or MEDI-493 group is > 1%). This table utilizes the COSTART designation.

Table 50. Severe or Life-threatening Adverse Events With an Incidence > 1% in Either Placebo Group or MEDI-493 Group

Event	Placebo n = 500		MEDI-493 n = 1002	
	Severe	Life-threatening	Severe	Life-threatening
Otitis Media	20 (4.0%)	0	20 (2.0%)	0
Diarrhea	11 (2.2%)	1 (0.2%)	21 (2.1%)	0
Gastroenteritis	11 (2.2%)	3 (0.6%)	13 (1.3%)	8 (0.8%)
Fever	11 (2.2%)	0	15 (1.5%)	1 (0.1%)
Hernia	9 (1.8%)	0	6 (0.6%)	0
Viral Infection	6 (1.2%)	1 (0.2%)	15 (1.5%)	0
Liver Function Test Abnormal	1 (0.2%)	1 (0.2%)	1 (0.1%)	10 (1.0%)*
Bronchiolitis	4 (0.8%)	3 (0.6%)	15 (1.5%)	1 (0.1%)
Pneumonia	11 (2.2%)	2 (0.4%)	11 (1.1%)	2 (0.2%)
Respiratory Disorder	7 (1.4%)	1 (0.2%)	6 (0.6%)	3 (0.3%)
Upper Respiratory Infection	6 (1.2%)	0	10 (1.0%)	1 (0.1%)

*P = 0.112, Fisher's Exact test

Comment: The 1% incidence of life threatening liver test abnormalities in the MEDI-493 group is of some concern. I will review these case report forms.

Overall, there was a total of 74 life-threatening AE (in 60 patients, 20 in placebo group and 40 in MEDI-493 group) and 358 severe AE (in 236 patients, 92 in placebo group and 144 in MEDI-493 group).

A total of 159 patients reported 240 AE that were judged by the investigators to be related to the study agent (possibly, probably or definitely. The number of patients were similar in the two trial arms (50, 10% in placebo group and 109 , 10.9% in MEDI-493 group). Severe or life-threatening AE related to the study agent were noted in 15 patients. These AE are shown in Table 51.

Table 51. Life-threatening and Severe Study Drug-related AE

Outcome	Placebo n = 500		MEDI-493 n = 1002	
	Severe	Life-threatening	Severe	Life-threatening
Total Number of Events	3	2	5	5
Total Patients Reporting One or More Events	2 (0.4%)	2 (0.4%)	5 (0.5%)	4 (0.4%)
Fever	1 (0.2%)	0	3 (0.3%)	0
Viral Infection	0	0	2 (0.2%)	0
SIDS	0	1 (0.2%)	0	0
LFT Abnormal	1 (0.2%)	0	0	3 (0.3%)
SGOT Increased	1 (0.2%)	0	0	1 (0.1%)
SGPT Increased	0	1 (0.2%)	0	1 (0.1%)

10.4.4 Adverse Events Resulting in Permanent Discontinuation of Study Drug:

The protocol required that investigators record the AEs leading to permanent discontinuation of the study drug. Six patients experienced 16 AEs which led to permanent discontinuation of the study drug. These data are shown in Table 52.

Table 52. Adverse Events Resulting in Permanent Discontinuation of Study Drug

Outcome	Placebo n = 500	MEDI-493 n = 1002
Total Number of Events	1	15
Total Patients Reporting One or More Events	1 (0.2%)	5 (0.5%)
Fever	0	2 (0.2%)
Injection Site Reaction	0	1 (0.1%)
Heart Failure	0	1 (0.1%)
Diarrhea	0	3 (0.3%)
Feeding Abnormality	0	1 (0.1%)
Gastroenteritis	1 (0.2%)	0
Melena	0	1 (0.1%)
Vomiting	0	2 (0.2%)
Anemia	0	1 (0.1%)
Hepatosplenomegaly	0	1 (0.1%)
Thrombocytopenia	0	1 (0.1%)
Nervousness	0	1 (0.1%)

Comment: In general, the review of AE that prompted permanent discontinuation of the study agent is unremarkable.

10.4.5 Fatalities:

Nine patients died during the study; five (1.0%) in the placebo group and four (0.4%) in the MEDI-493 group. The protocol required the site investigator to assign an etiology as the cause for the death and state whether the death was related to the study agent.One fatality was attributed by the site investigator to the study agent (placebo, SIDS). One fatality were attributed to RSV disease. This fatality occurred during an RSV hospitalization and the patient was in the MEDI-493 group. Table 53 shows mortality data.

Table 53. Fatalities

Group and Patient number	Cause of Death	Study Day of Death
Placebo		
	SIDS	86
	BPD complications	28
	Non-RSV bronchopneumonia	52
	SIDS	118
	pneumococcal sepsis	0
MEDI-493		
	RSV pneumonia	38
	Non-RSV pneumonia	19
	SIDS	30
	Deterioration after PE tube surgery during RSV hospitalization	68

Comment: It is notable that the only deaths that occurred during an RSV hospitalization, occurred among two patients in the MEDI-493 group.

10.4.6 Serious Adverse Events:

The protocol also required the reporting of AE as "serious." Serious AE (SAE) included those which were fatal, life-threatening, permanently disabling, required or prolonged hospitalization, included cancer, overdose or graded as grade three or four toxicity according the protocol's toxicity table. The protocol also required the site investigator to assign a causality assessment to each SAE. A total of 468 patients reported 752 serious AE. The proportions of patients experiencing SAE was similar in the two trial arms (170, 34.0% in the placebo group and 298, 29.7% in the MEDI-493 group). Table 54 shows all SAE

associated with an incidence that was higher in the MEDI-493 group than in the placebo group.

Table 54. Serious Adverse Events with an Incidence Higher in MEDI-493 Group

SAE	Placebo n = 500	MEDI-493 n = 1002
Bronchiolitis	24 (4.8%)	50 (5.0%)
Hernia	17 (3.4%)	37 (3.7%)
Fever	9 (1.8%)	21 (2.1%)
LFT abnormal	2 (0.4%)	11 (1.1%)
Dyspnea	4 (0.8%)	10 (1.0%)
Failure to thrive	2 (0.4%)	6 (0.6%)
Vomiting	0	5 (0.5%)
Intestinal obstruction	1 (0.2%)	4 (0.4%)
Hydrocephalus	0	3 (0.3%)
Convulsion	0	3 (0.3%)
Hypoxia	0	2 (0.2%)
Infection (body as a whole)	0	2 (0.2%)
Overdose	0	2 (0.2%)
Allergic reaction	0	1 (0.1%)
Clubfoot	0	1 (0.1%)
Granuloma	0	1 (0.1%)
Hypertrophy (body as a whole)	0	1 (0.1%)
Peritonitis	0	1 (0.1%)
Vascular anomaly	0	1 (0.1%)
Heart failure	0	1 (0.1%)
Abdomen enlarged	0	1 (0.1%)
Cholecystitis	0	1 (0.1%)
Cleft lip	0	1 (0.1%)
Dysphagia	0	2 (0.2%)
Enteritis	0	1 (0.1%)
Hepatitis	0	1 (0.1%)
Melena	0	1 (0.1%)
Intestinal stenosis	0	1 (0.1%)
Thrombocytopenia	0	1 (0.1%)
CPK increased	0	1 (0.1%)
Hypervolemia	0	1 (0.1%)
Hypokalemia	0	1 (0.1%)
Mental retardation	0	1 (0.1%)
Hyperventilation	0	1 (0.1%)
Hypoventilation	0	1 (0.1%)
Strabismus	0	1 (0.1%)

Seventeen patients experienced 19 SAEs judged by the investigator to be possibly, probably or definitely related to the study drug. These SAE are summarized in Table 55.

Comment: It is notable that 11 patients had LFT abnormalities reported as SAE. Only one of these patients had a remarkably elevated blood MEDI-493 level recorded. Patient number had a MEDI-493 blood level of 487.05 mcg/mL obtained at the time of the fourth injection. In general, the serious LFT abnormalities do not seem related to accumulation of MEDI-493 in the blood. It is notable that many of these infants were maintained on parenteral nutrition and had multiple reasons for LFT abnormalities. In general, it appears unlikely MEDI-493 was related to the liver abnormalities.

Table 55. SAE Considered to be Related to Study Drug

Outcome	Placebo n = 500	MEDI-493 n = 1002
Total Number of Related SAE	5	14
Total Patients Reporting One or More Related SAE	4 (0.8%)	13 (1.3%)
Fever	1 (0.2%)	4 (0.4%)
Viral infection	0	2 (0.2%)
Overdose	0	2 (0.2%)
SIDS	1 (0.2%)	0
LFT Abnormal	1 (0.2%)	3 (0.3%)
SGOT increased	1 (0.2%)	1 (0.1%)
SGPT increased	1 (0.2%)	1 (0.1%)
Bronchiolitis	0	1 (0.1%)

Comment: Again, these data are notable for the slightly higher incidence of liver function abnormalities in the MEDI-493 group.

10.4.7 Immunizations during the study:

Patients were to receive all regularly scheduled immunizations. Table 56 summarizes the number of immunizations administered.

Table 56. Number of Immunizations

Vaccine	MEDI-493 n = 1,002	Placebo n = 500
Hepatitis	395 (39.4%)	196 (39.2%)
Morbilli	63 (6.3%)	35 (7.0%)
Polio	584 (58.3%)	269 (53.8%)
DTP	683 (68.2%)	319 (63.8%)
TB	1 (0.1%)	0
Varicella	21 (2.1%)	11 (2.2%)

Comment: Many routine immunizations were given during this study without any notable safety signals.

11.0.0 Conclusions:

Comments:

The sponsor has developed MEDI-493 as an agent to be utilized to prevent RSV illness. The preclinical and clinical assessments support the safety and efficacy of MEDI-493 and it is recommended for licensure.

The assessment of efficacy was based upon the ability of MEDI-493 to lower the RSV hospitalization rate. The sponsor performed a large phase 3 study which showed that the relative risk for RSV hospitalization could be lowered by approximately 55% in infants at high risk for RSV disease. The following points are notable:

- Efficacy: The sponsor has demonstrated that MEDI-493 is effective in the prevention of RSV illness. The decrease in the RSV hospitalization rate shows that MEDI-493 decreases the severity of RSV illness. It is notable that patients who were treated with MEDI-493 but who required hospitalization for RSV (prophylaxis failures) were not less critically ill than the placebo patients who were hospitalized. Hence, MEDI-493 appears most effective in decreasing the incidence of less critically severe RSV illnesses. It will be important for the label to not imply that MEDI-493 decreases the severity of RSV illness among prophylaxis failures.

- Dose: The sponsor performed minimal dose ranging studies and the chosen dose is based upon animal pharmacodynamic data. It is not known whether higher doses would result in greater efficacy. A single IV dose in adult volunteers at twice the recommended MEDI-493 prophylaxis dose has been shown to be well tolerated. The sponsor's phase 3 study demonstrates the efficacy of the proposed dose. The sponsor's dose selection is adequate.

- Safety: The sponsor has shown MEDI-493 to be well tolerated. There were many adverse events in the phase 3 study, but all notable events appeared related to the underlying illness. The incidence of mechanical ventilation among MEDI-493 prophylaxis failures was higher than that among the placebo group . However, the incidence was not statistically higher . This observation reinforces the observation that there no data suggest that MEDI-493 decreases the severity of illness among prophylaxis failures.

- Recommendations regarding phase 4 studies: The sponsor should propose a registry follow-up study of patients who are treated with MEDI-493 and who undergo RSV hospitalization. The goal of this study should be to detect RSV isolates that are not neutralized by MEDI-493. This study should be conducted over several years.

  Additionally, the sponsor should propose a safety study of the use of MEDI-493 in the prophylaxis of infants with congenital heart disease. This study might result in a limited modification of the label.